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REJECTIONS UNDER 35 U.S.C. §112

Claim 39 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to provide a definition of histone analogs or to define the genus of histone analogs. In this regard, the Office Action asserts that it is unclear which proteins would be considered a histone analog.

Applicant submits that the meaning of the term is clear in light of the description in the specification as well as that which is well known in the art. Histones are well known in the art. They have been the subject matter of many studies over the years and can be found described in many molecular or cell biology text books. Exemplary publications supporting that they are well known in the art include, for example, Meyers, R.A., *Molecular Biology and Biotechnology, A Comprehensive Desk Reference*, VCH Publishers, Inc., 413-17, (1995), and Lodish, H. et al., *Molecular Cell Biology*, Scientific American Books, 3rd Ed., 315-16, 346-348, (1995), attached hereto as Exhibits A and B, respectfully.

Further, the specification describes, for example, at pages 44-50 the use of histone H2B in various studies to label chromosomes by expression. Within these descriptions, histone H2B is labeled at either the amino- or carboxy-terminus with, for example, GFP (green fluorescent protein). Further described is the association of histone H2B in nucleosomes and its relationship as a H2A/H2B dimer with histone H1 and histone H3/H4 tetramer. Accordingly, the specification sufficiently

supports the use of labeled histones in the method of the invention.

Similarly, amino acid and polypeptide analogs also are well known in the art. For example, amino acid analogs include modified forms of naturally and non-naturally occurring amino acids. Naturally occurring amino acids include the 20 (L)-amino acids utilized during protein biosynthesis as well as others such as 4-hydroxyproline, hydroxylysine, desmosine, isodesmosine, homocysteine, citrulline and ornithine, for example. Non-naturally occurring amino acids include, for example, (D)-amino acids, norleucine, norvaline, p-fluorophenylalanine, ethionine and the like. Modifications can include, for example, substitution or replacement of chemical groups and moieties on the amino acid or by derivitization or alternative synthesis of the amino acid.

Specific examples of amino acid analogs can be found described in, for example, Roberts and Vellaccio, *The Peptides: Analysis, Synthesis, Biology*, Eds. Gross and Meinhofer, Vol. 5, pp. 341-358, Academic Press, Inc., New York, New York (1983), which is attached hereto as Exhibit C. Other examples include peralkylated amino acids, particularly permethylated amino acids, which can be found described in, for example, *Combinatorial Chemistry*, Eds. Wilson and Czarnik, Ch. 11, pp. 235-237, John Wiley & Sons Inc., New York, New York (1997), attached as Exhibit D. Yet other examples include amino acids whose amide portion (and, therefore, the amide backbone of the resulting peptide) has been replaced, for example, by a sugar

ring, steroid, benzodiazepine or carbo cycle. An exemplarly description of these analogs can be found described in, for example, *Burger's Medicinal Chemistry and Drug Discovery*, Ed. Manfred E. Wolff, Ch. 15, pp. 619-627, John Wiley & Sons Inc., New York, New York (1995), attached as Exhibit E.

In light of the teachings and guidance in the specification as well as the well known meaning in the art, Applicant maintains that the objected term is sufficiently clear to allow those skilled in the art to practice the invention as claimed. Accordingly, withdrawal of this ground of rejection is respectfully requested.

REJECTIONS UNDER 35 U.S.C. §103

Claims 33-38, 42-50, 53 and 54 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Robinett et al. in view Abken et al. Robinett et al. is stated to describe a method for visualizing chromosomes by expressing a GFP-lac repressor-nuclear localization signal fusion protein. Abken et al. is stated to describe extrachromosomal DNA and double minute DNA as being chromosomal in origin. The Office Action alleges that it would have been obvious to use the visualization method described by Robinett et al. in a method for identifying agents that decrease or increase double minute chromosome formation. The rational provided for increasing double minute chromosome formation is allegedly because they are associated with carcinogenesis.

To establish a prima facie case of obviousness, the Office must show that the prior art would have suggested the claimed device to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success when viewed in the light of the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000). The first requirement of this test is at issue in the claimed invention because the Office Action simply asserts that it would have obvious to use chromosome visualization to identify agents that decrease the amount of double minute (DM) chromosomes. Further, the reasoning that identifying agents which increase DM chromosomes because they are associated with carcinogenesis is unclear. The Office has failed to show that such general conclusions are supported by the cited art.

Establishing that the prior art would have suggested the claimed device requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an "essential evidentiary component of an obviousness holding." *Brown & Williamson Tobacco*, 229 F.3d at 1124-25 (*quoting C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1351-52 (Fed.Cir.1998); *see also C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art where to select the components that the inventor selected and use them to make the new device); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) (there must be some motivation, suggestion or teaching in the prior art of the desirability of making the specific combination that was made by the applicant). The evidentiary showing must be clear and

particular and broad conclusory statements about the teachings of the cited references, standing alone, are not "evidence." *Brown & Williamson Tobacco*, 229 F.3d at 1125 (*quoting In re Dembiczak*, 175 F.3d 994, 1000 (Fed.Cir.1999), abrogated on other grounds by *In re Gartside*, 203 F.3d 1305, 53 USPQ2d 1769 (Fed.Cir.2000)).

In the pending Office Action, there has been no underlying factual showing that it would have been obvious to one of ordinary skill in the art to have modified the alleged visualization method of Robinett et al. with the description of Abkin et al. to obtain the claimed screening method. The Office has failed to point to clear and particular language suggesting use of any method to screen for agents that alter the amount of chromosomal DNA much less DM DNA. Robinett et al. appears to be directed to chromosomal visualization methods. Further, Robinett et al. states that future applications of their method should "facilitate structural, functional, and genetic analysis of chromosome organization, chromosome dynamics, and nuclear architecture" (abstract, last sentence). These suggested future applications do not mention screening, and as such, Robinett et al. appears to be unconcerned with screening. Therefore, the assertion in the Office Action appears to be nothing more than a conclusory statement, unfounded by supporting evidence. Accordingly, the Office has not established its burden that the showing of a suggestion, motivation or teaching of the claimed combination must be clear and particular.

One purpose of the evidentiary requirement for showing a suggestion, motivation or teaching of the claimed combination is to prevent impermissible hindsight reconstruction of the claimed invention based on Applicant's own disclosure. *C.R. Bard*, 157 F.3d at 1352; *In re Dembiczak*, 175 F.3d 994, 999 ("[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight"). In determining the validity of patented biopsy needle assembly over the sole assertion that it arose from obvious adaptations of a single prior art needle assembly to accommodate a new biopsy gun design, the court admonished against hindsight reconstruction when it stated:

> The invention that was made, however, does not make itself obvious; that suggestion or teaching must come from the prior art. *See, e.g., Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051-52, 5 USPQ2d 1434, 1438 (Fed.Cir.1988) (it is impermissible to reconstruct the claimed invention from selected pieces of prior art absent some suggestion, teaching, or motivation in the prior art to do so); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed.Cir.1985) (it is insufficient to select from the prior art the separate components of the inventor's combination, using the blueprint supplied by the inventor); *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556, 225 USPQ 26, 31 (Fed.Cir.1985) (the prior art must suggest

to one of ordinary skill in the art the desirability of the claimed combination).

The court went on to conclude that because no prior art provided a teaching, suggestion or motivation for the structure of the claimed needle assembly there was, as a matter of law, an absence of an essential evidentiary component for an obviousness finding. *C.R. Bard* at 1352.

Similarly, here, the Office Action has taken Applicants' own teachings and used it against them without additional support that the prior art would have suggested, motivated or taught one of ordinary skill to make the claimed combination. As describe above, Robinett et al. appears to have been unconcerned with methods to screen for agents that alter the amount of DM DNA. Similarly, Abken et al. also does not suggest screening for agents that alter the amount of DM DNA. Instead, Abken et al. is alleged to describe that DM DNA is chromosomal in origin and that it may cause disregulation of cancer cell growth.

The Office Action neither cites art showing a combination of chromosome visualization with screening methods nor cites to text in the cited references that provide a suggestion, motivation or teaching to achieve the claimed combination. The alleged rational fails to support any motivation because there is no evidence that either Robinett et al. or Abken et al. considered screening for agents of any kind.

Reliance on "common knowledge and common sense" to fill the void for the required showing of a suggestion for a claimed combination of elements does not substitute for the obligation to cite references to support an obvious conclusion. *In re Thrift*, 298 F.3d 1357, 1364 (Fed. Cir. 2002). Consequently, such a lack of an evidentiary showing is nothing more than impermissible hindsight reconstruction based on reading Applicant's own invention and reliance on unsupported conclusory statements. Applicants therefore respectfully request that the rejection of claims 33-36, 39-50, 53 and 54 be withdrawn.

CONCLUSION

In light of the Remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

Respectfully submitted,

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Molecular Biology and Biotechnology

A Comprehensive Desk Reference

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EXHIBIT A

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Management Supervised by:
Chernow Editorial Services, Inc.,
1133 Broadway, Suite 721, New York, NY, USA

Cover design by: G & H SOHO, Inc.

Cover art courtesy of Dr. Alexander Wlodawer from Figure 1 of his article,
"AIDS, Inhibitor Complexes of HIV-1 Protease in."
Art prepared by Dr. Jacek Lubkowski.

Library of Congress Cataloging-in-Publication Data

Molecular biology and biotechnology : a comprehensive desk reference /
Robert A. Meyers, editor.
p. cm.
Includes bibliographical references and index.
ISBN 1-56081-569-8 (alk. paper). — ISBN 1-56081-925-1 (pbk.: alk. paper)
1. Molecular biology—Encyclopedias. 2. Biotechnology—Encyclopedias.
I. Meyers, Robert A. (Robert Allen), 1936-
QH506.M66155 1995
574.8'8'03—dc20 95-9063
CIP

Printed in the United States of America

ISBN 1-56081-569-8 (hardcover)

Printing History:
10 9 8 7 6 5 4 3 2

ISBN 1-56081-925-1 (softcover)

Printing History:
10 9 8 7 6 5 4 3 2

Published jointly by:

VCH Publishers, Inc.
220 East 23rd Street
New York, NY 10010
USA

VCH Verlagsgesellschaft mbH
P.O. Box 10 11 61
D-6940 Weinheim
Federal Republic of Germany

VCH Publishers (UK) Ltd.
8 Wellington Court
Cambridge CB1 1HW
United Kingdom

Fax: (212) 481-0897
E-mail address: order@vch.com

...lies either because of lack of informative markers or because ...certainties about when the hemophilia mutation had arisen in ...e family.

In hemophilia B, the development of rapid methods for detecting virtually all hemophilia B mutations now allows diagnoses based on the direct detection of the gene defect and ensures success in virtually every family (Figure 3b). In the United Kingdom a national strategy is being implemented for the provision of genetic counseling. This entails the construction of a national confidential database of mutation, hematological, and pedigree information that can be used to provide carrier and prenatal diagnosis to the blood relatives of the patients listed in the database by examination of the region of the gene defective in the index patient. This allows precise, rapid, and economical diagnoses. Similar developments in hemophilia A may occur later, in spite of the size and complexity of the factor VIII gene. The inversion mutations involving intron 22 are now the easiest to identify. Rapid methods begin to be available for the detection of the remaining hemophilia A mutations.

See also GENETIC TESTING; HUMAN DISEASE GENE MAPPING.

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HISTONES

Gary S. Stein, Janet L. Stein, and André J. van Wijnen

Key Words

Cell Cycle The interval between the completion of mitosis in the parent cell and the completion of the next mitosis in one or both progeny cells. The periods of the cell cycle are sequentially defined as mitosis (prophase, metaphase, anaphase, and telophase), G_1 (the period between the completion of mitosis and the onset of DNA replication), S phase (the period of the cycle during which DNA replication occurs), and G_2 (the period between the completion of DNA replication and the onset of mitosis).

Histone Proteins Five principal species of basic chromosomal proteins designated H2a, H2b, H3, H4, and H1, which range in size from 11,000 to 25,000 Da. Histone proteins complex with DNA to form the primary unit of chromatin structure, the nucleosome.

Nucleosome The primary unit of chromatin structure in eukaryotic cells, consisting of approximately 200 nucleotide base pairs of DNA and two each of the core histone proteins (H2a, H2b, H3, and H4).

Posttranscriptional Control The components of gene expression involving regulation mediated at the level of messenger RNA processing within the nucleus and/or cytoplasm, the translatability and/or stability of mRNA, or the assembly or posttranslational modifications of polypeptides.

Promoter Regulatory Elements DNA sequences, generally but not necessarily, 5′ (upstream) from the mRNA transcription initiation site, which modulate the specificity and/or level of transcription.

Transcriptional Control The component of gene expression involving the synthesis of RNA, utilizing DNA as a template.

Histones are positively charged nuclear proteins that are ubiquitously represented in eukaryotic cells for packaging DNA into the protein–DNA complex termed chromatin. Histone–DNA complexes form the primary unit of chromatin structure, the nucleosome. Modifications in the interactions of histones with DNA in specific regions of genes occur in association with changes in gene expression. Mammalian and nonmammalian histone genes have been cloned and characterized with respect to the regulation of expression. The histone genes are a multigene family, and most are expressed in proliferating cells at the time in the cell cycle when DNA is replicated, providing histone proteins to package newly replicated DNA into chromatin. Other histone genes are expressed postproliferatively to support structural and transcriptional requirements of specialized cells. Regulatory sequences of histone genes, which determine the specificity of levels of transcription, as well as factors that bind to regulatory elements to mediate histone gene expression, have been identified.

1 GENERAL CHARACTERISTICS

1.1 THE BIOLOGICAL AND STRUCTURAL PROPERTIES OF HISTONE PROTEINS

There are five principal species of histone proteins, designated H2a, H2b, H3, H4, and H1, ranging in size from 11,000 to 25,000 Da. They are positively charged, as a result of high contents of the basic amino acids arginine, lysine, and histidine, which facilitate the interactions of histones with negatively charged DNA molecules. The amino acid sequences of the histone proteins have been highly conserved during evolution, reflecting the conserved role of these proteins in chromatin structure and the apparently stringent requirement to support conservation of the primary unit of chromatin structure, the nucleosome.

The histone proteins are encoded in a multigene family with multiple (e.g., approximately 20 copies in human cells), nonidentical copies of each core (H2a, H2b, H3, and H4) and H1 gene. The histone polypeptides can be separated into the following categories:

1. Those that are represented in most cells and tissues and synthesized only in proliferating cells at the time of DNA synthesis (> 90%).
2. Those that are found in many cells and tissues but are expressed independently of proliferation, either constitutively during the cell cycle or following the completion of proliferation at the onset of tissue-specific gene expression associated with differentiation.
3. Those that are expressed solely in specialized cell types, such as spermatocytes and avian erythrocytes, in which there are

highly specific requirements for modifications in the packaging of DNA into chromatin. In lower eukaryotes, and apparently only in these organisms, there are multiple copies of the histone genes, providing large quantities of "stored" histone mRNA in oocytes that can support histone protein synthesis during the rapid series of initial cell divisions that immediately follows fertilization.

Additional heterogeneity of the histone proteins is reflected by posttranslational modifications that include acetylation, methylation, phosphorylation, and adenosine diphosphate (ADP) ribosylation. Such modifications alter the distribution of charge in specific domains of the histone proteins and, together with hydrophobic bonding, may influence histone–DNA as well as histone–histone interaction. These posttranslational modifications are involved in the incorporation of newly synthesized histones into chromatin and may provide a basis for changes in the interactions of histones with DNA for remodeling chromatin architecture: for example, in condensation of chromatin into discrete chromosomes at the onset of mitosis, and in modification of chromatin structure when the expression of specific genes is activated or repressed. These changes in histone-mediated chromatin structure are rapid and reversible, supporting cellular responsiveness to a broad spectrum of physiological signals that mediate transcription of cell growth, housekeeping, and tissue-specific genes.

1.2 The Contribution of Histones to Chromatin Structure

There is a requirement for the ordered packaging of 2.5 yards of DNA within the confines of the mammalian cell nucleus. To accommodate this DNA packaging into nucleosomes, every nucleus contains approximately 300 million histone molecules. Each nucleosome consists of a core particle of approximately 140 base pairs of DNA wound around a complex consisting of two H2a, H2b, H3, and H4 molecules and a linker DNA region of approximately 40–60 base pairs (Figure 1). Under the electron microscope, the nucleosomes appear as a series of beads (protein–DNA complexes) on a string (linker DNA joining the nucleosomes). The H1 histones bind to the linker region and participate in nucleosome–nucleosome interactions. This organization accounts for only a 10 nm chromatin fiber and a packing ratio of 7. The 10 nm beads-on-a-string structures are packed as a 30 nm chromatin fiber, and further packaging results in chromatin fibers of 100 nm. "Nonhistone," sequence-specific DNA binding proteins can mediate DNA conformation and modulate histone–DNA interactions. Thus, it appears that the contributions of histones to transcriptional regulation are through facilitation of conformational properties of DNA that are responsive to gene-specific transcription factors.

2 EXPRESSION OF HISTONE GENES

A functional, as well as temporal, relationship between DNA replication and the expression of mammalian core and H1 histone genes was initially indicated by the constant histone–DNA ratio (1:1) observed in a broad spectrum of cells, tissues, and organs, and by the doubling of cellular levels of histone protein during the S phase of the cell cycle. Direct measurements then confirmed that histone protein synthesis is largely confined to S phase and that inhibition of DNA replication results in a rapid cessation of histone protein synthesis. The cellular levels of histone mRNA reflect cellular

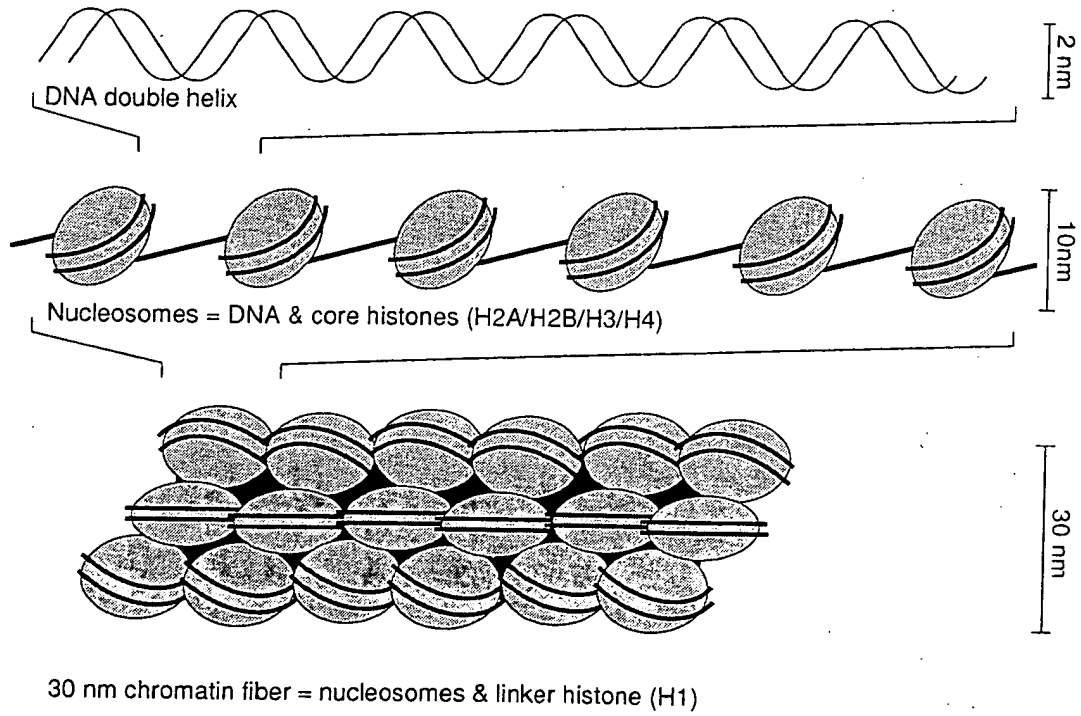

Figure 1. Three principal levels of chromatin organization. *Top:* The 2 nm, deproteinized, double-stranded DNA double helix. *Middle:* The organization of DNA into nucleosomes. The beads-on-a-string structure comprises a 10 nm fiber; each bead consists of two each of core histone proteins (H2A, H2B, H3, and H4). The string component of the structure is the DNA. *Bottom:* The higher order organization of chromatin structure mediated by association of nucleosomes through linker histone H1 into a 30 nm chromatin fiber.

levels of both histone protein synthesis and DNA replication. Similarly, inhibition of DNA replication brings about a dose-dependent loss (selective destabilization) of histone mRNAs, which parallels decreases in DNA and histone synthesis. Measurements of histone gene transcription indicate enhanced synthesis of histone mRNAs early during the S phase of the cell cycle.

The increased transcription of histone genes early during S phase and the coordinate accumulation of histone mRNAs for core and H1 histone proteins that closely parallels the initiation of DNA and histone protein synthesis suggest that the onset of histone gene expression is at least in part transcriptionally mediated. Throughout S phase, the synthesis of histone proteins is modulated by the availability of histone mRNAs. The stabilization of histone mRNAs throughout S phase and the destabilization of histone mRNAs when DNA replication is completed or inhibited are highly selective, and largely posttranscriptionally controlled. At the onset of differentiation in mammalian cells, the histone genes that are under cell cycle regulation are down-regulated transcriptionally. When DNA replication is completed during the terminal cell cycle, histone protein synthesis ceases, histone mRNA is degraded, and both basal and enhanced levels of histone gene transcription are abrogated.

3 ORGANIZATION AND REGULATION OF HISTONE GENES

3.1 Organization of Cell-Cycle-Regulated Histone Genes

In mammalian cells, the cell-cycle-regulated histone genes are organized into clusters of core alone (H2a, H2b, H3, and H4) or core together with H1 histone coding sequences (Figure 2). Within these clusters, which are represented on at least two chromosomes, there is generally a pairing of H2a with H2b genes and H3 with H4 genes. In lower eukaryotes such as sea urchin and *Drosophila*, a similar organization is found for the cell-cycle-regulated genes encoding somatic cell histone proteins. However, the histone genes expressed during oogenesis in these organisms are organized as simple, tandemly repeated clusters that contain one of each of the five types of histone gene.

Despite the clustering of cell-cycle-regulated histone genes, each histone coding sequence is an independent transcription unit with a unique promoter and mRNA coding sequence. All amino acids of the histone protein are encoded in contiguous nucleotides because these genes lack introns. Also noteworthy are the absence of a polyadenylation site and the presence of sequences with hyphenated dyad symmetry that form a stem–loop structure in the 3′ region as well as nontranslated leader and trailer segments of the mRNA that are less than 50 nucleotides long.

3.2 Promoter Elements and Transcription Factors That Regulate Cell-Cycle-Dependent Histone Gene Expression

Figure 3 is a schematic representation of the regulatory organization of the initial thousand base pairs of an H4 histone gene promoter. While this region contains the minimal sequences required for regulated expression, the functional limits of the H4 gene appear to extend considerably upstream. Indeed, cis-acting elements up to −6.5 kB may influence developmental expression of the H4 histone gene in vivo in transgenic animals. Two domains of in vivo protein–DNA interactions for the H4 histone gene have been established in the intact cell at single nucleotide (nt) resolution. These have been designated H4-site I (nt −156 to −113) and H4-site II (nt −97 to −47). The proximal promoter domain H4-site I is a bipartite cis-activating element that interacts distally with a member of the ATF family of transcription factors, and proximally with the GC box binding protein (Sp1) HiNF-C. These factors are capable of mediating a fivefold stimulation of transcription. The H4-site II domain represents a mosaic of functional recognition sequences that contribute to H4 gene transcription. H4-site II is a multipartite protein–DNA interaction site for sequence-specific

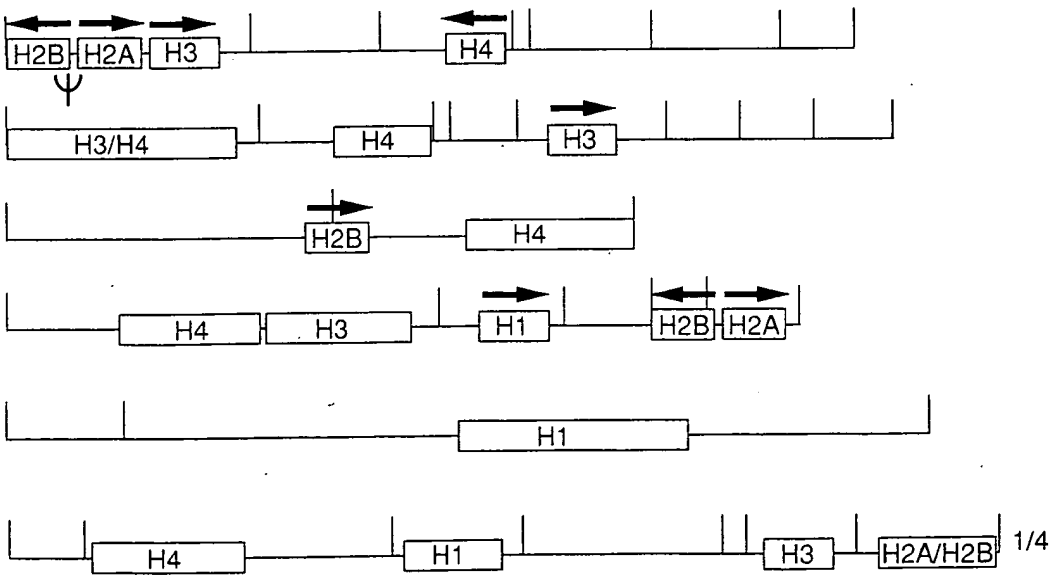

Figure 2. The organization of genomic DNA segments containing some of the human histone coding sequences; Arrows designate directions of transcription. H2B and H2A pseudogenes are designated by the symbol Ψ.

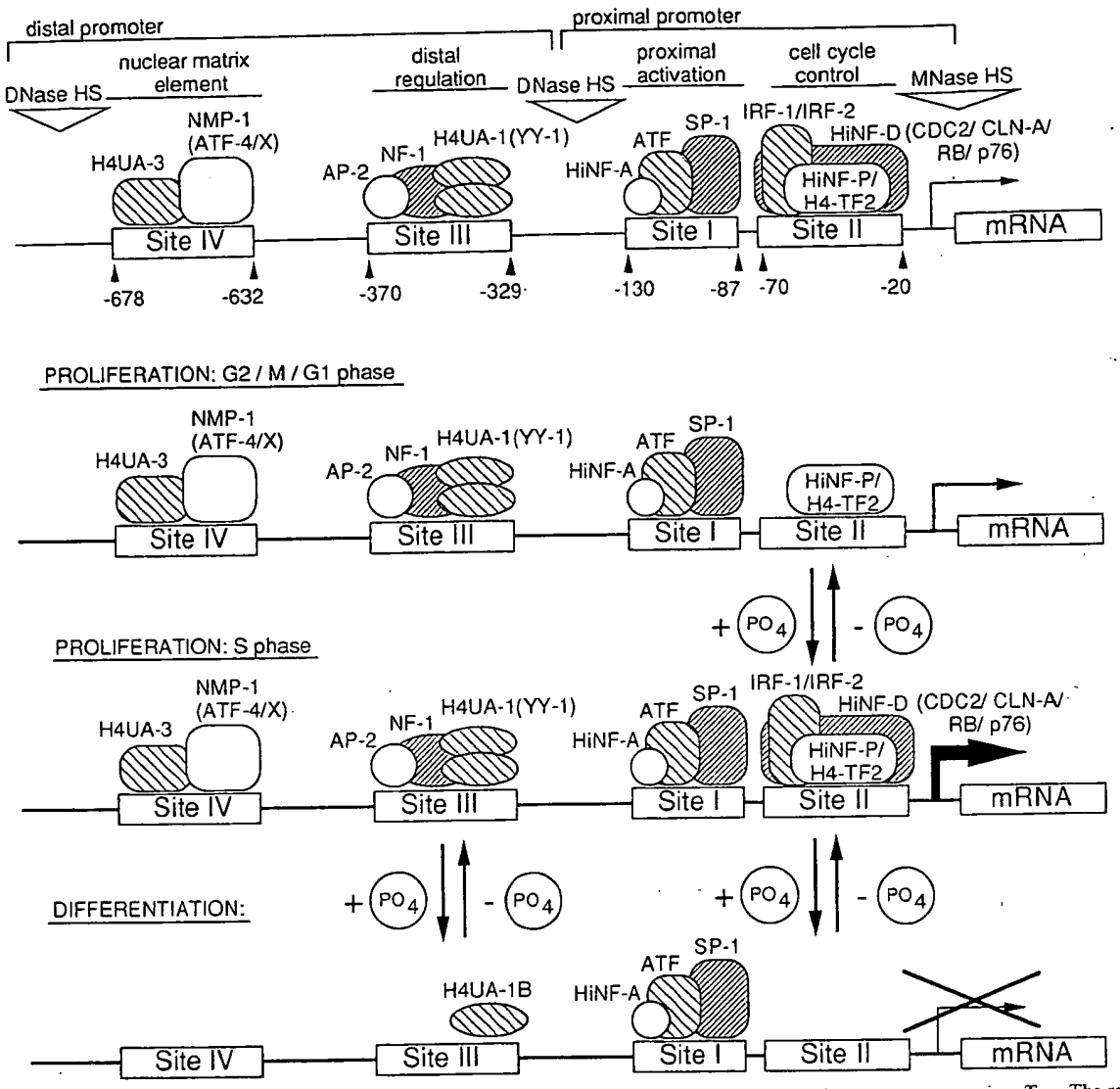

Figure 3. Schematic representation of promoter regulatory elements and transcription factors that support histone gene expression. *Top:* The representation and organization of gene regulatory sequences is designated by sites I–IV. The ovals and boxes represent transcription factors. Proximal and distal cell cycle regulatory elements are designated along with nuclease sensitive regions (DNase HS, MNase HS). Also shown are sites of histone gene interactions with the nuclear matrix. *Three lower segments:* Phosphorylation-dependent modifications in interactions of transcription factors with histone gene promoter elements both during the cell cycle and following differentiation. These modificatons in protein–DNA interactions control the extent to which the histone gene is transcribed, which is indicated by the thickness of the horizontal arrows over the mRNA regions of the gene.

factors HiNF-D, HiNF-M, and HiNF-P (H4-TF2). The proximal region of H4-site II spans a TATA motif and is sufficient to mediate accurate transcription initiation in vivo. However, the distal region of H4-site II influences transcriptional competency, as well as the timing and extent of H4 mRNA synthesis in vivo. This site II distal region contains several distinct sequence motifs that either stimulate the basal level of H4 gene transcription (C box) or influence periodic levels of transcription (M box). The distal activating elements H4-sites III and IV encompass regions that stimulate transcription in vivo and interact with the heteromeric nuclear factors H4UA-1 and H4UA-3, respectively. Additionally, H4-site IV overlaps with a putative nuclear matrix attachment site spanning nt −730 to −589. This element interacts with a sequence-specific nuclear matrix protein (NMP-1), and may influence expression of the H4 histone gene promoter by transient anchorage to the nuclear matrix. The integration of mechanisms controlling the coordinately regulated transcription of multiple histone genes may involve several shared promoter-binding activities, including both ubiquitous and histone-gene-specific transcription factors. HiNF-D related protein–DNA interactions are also represented in H3 and H1 histone gene promoters, suggesting the possibility of coordinate transcription factor interactions regulating several histone gene classes.

Insight into transcriptional control of histone gene expression has been provided by identification of modifications in interactions of promoter binding factors within the initial thousand base pairs of a human H4 histone gene promoter at sites I, II, III, and IV, and relating these to the extent of gene transcription. Protein–DNA interactions at these regulatory elements during the cell cycle and with the down-regulation of proliferation during differentiation are schematically shown in Figure 3.

See also CHROMATIN FORMATION AND STRUCTURE; GENE EXPRESSION, REGULATION OF; PROTEIN DESIGNS FOR THE SPECIFIC RECOGNITION OF DNA.

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HIV: *see* AIDS articles.

HPLC OF BIOLOGICAL MACROMOLECULES

Karen M. Gooding

Key Words

Bonded Phase Organic coating or layer covering the surface of the solid HPLC support and containing the functional groups responsible for separation.

Elution Process of a solute passing through and coming out of a chromatography column.

Gradient Systematic variation of the mobile phase composition during an HPLC analysis.

Packing Adsorbent, gel or solid support used in the HPLC column.

High performance liquid chromatography (HPLC) is a high resolution separation process using a liquid mobile phase and a column containing microparticulate solid particles coated with a specific functional group. The functional groups, which can be neutral, charged, or hydrophobic, cause separation of components of a mixture by the specific physical interaction. The primary modes of HPLC for biological macromolecules are reversed phase, ion exchange, size exclusion, and hydrophobic interaction chromatography. These rapid and high resolution methods have provided a means of purification, separation, and analysis of peptides and proteins in biotechnology, microbiology, university, and clinical laboratories.

1 INTRODUCTION

Liquid chromatography is a separation process in which the components in a mixture migrate in a liquid stream through a packed bed of particles that retard some of the components differentially by a specific physical property. The particles that compose the column have a uniform physical characteristic, such as hydrophobicity, charge, or porosity, which brings about separation by causing molecules or ions to interact or pass through at different rates.

Liquid chromatography has been an important method of separating and purifying proteins and nucleic acids because these substances are soluble and often stable in aqueous buffers. For many years, methods utilized columns containing carbohydrate matrices that achieved good separations in hours or days; flow rates were slow because they were based on gravity. In the mid-1970s, rigid packing materials composed of silica or polymer with diameters of 5 to 10 μm were developed to be used with liquids pressured to several thousand psi. This technique, initially known as high pressure liquid chromatography, is now called high performance liquid chromatography (HPLC). Chemical modification of the surface of the silica or gel support, known as the bonded phase, gives the specific basis for retention.

Columns placed with microparticulate HPLC supports can separate biological macromolecules in minutes with excellent resolution and recovery of biological activity. Since the 1970s, both the technology of producing HPLC columns and the understanding of their operation have improved dramatically, resulting in the widespread use of HPLC for protein and peptide analysis and purification. Although biological macromolecules include polypeptides, polynucleotides, and polysaccharides, this entry primarily discusses polypeptides because of the vast amount of research on the subject. The principles are generally applicable to biomolecules in all three categories.

2 INSTRUMENTATION

2.1 General

A high performance liquid chromatograph consists of one or more pumps, a sample injector, a column, a detector, and a data recorder. If a single solvent is used as the mobile phase, the method is termed *isocratic.* In many cases, more than one solvent must be used to release the bound molecules and cause them to elute from the column. Multiple solvents are usually combined in a programmed gradient from one composition to another. The time and variation of composition is called the gradient. Figure 1 illustrates the typical configuration of an HPLC with two pumps.

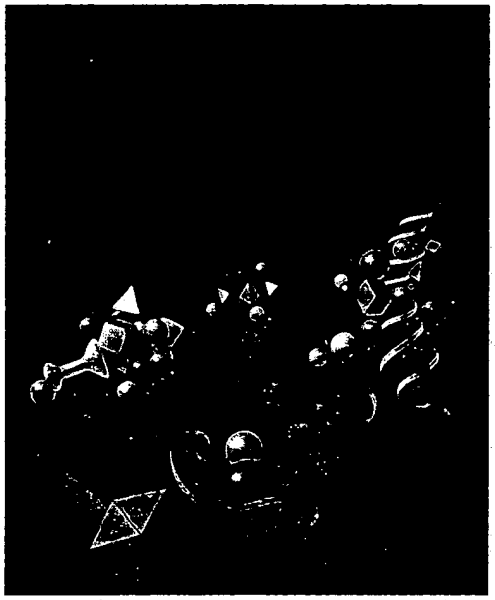
2.2 Columns

The column is the key element of the HPLC system. The physical process by which the molecules bind will determine which mobile phase will promote binding and which will release, thereby causing elution. The packing material, or support, in the column is composed of a rigid material, such as silica or a polymer, which can be derivatized or covalently bonded with functional groups; this chemical layer is called the bonded phase. HPLC supports usually have particle diameters of 5 to 10 μm and may be porous or nonporous. For biological macromolecules, pores must be at least 300 A in diameter to allow access, whereas small molecules are typically run on supports with pores of 80 to 100 A diameters.

2.3 Detectors

Detectors for HPLC tend to be selective rather than general. Refractive index detectors, which produce a signal for all solutes, are the primary devices used, but their sensitivity is low. Light-scattering or "mass" detectors are not very sensitive and have nonlinear

MOLECULAR CELL



BIOLOGY

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SCIENTIFIC AMERICAN BOOKS

An Imprint of W. H. Freeman and Company, New York

EXHIBIT B

Cover illustration by Nenad Jakesevic

Library of Congress Cataloging-in-Publication Data

Molecular cell biology/James Darnell . . . [et al.].—3d ed.
p. cm.
Second edition's main entry under the heading for Darnell.
Includes bibliographical references and index.
ISBN 0-7167-2380-8
1. Cytology. 2. Molecular biology. I. Darnell, James E.
QH581.2.D37 1995 94-22376
574.87'6042—dc20 CIP

Printed in the United States of America

Scientific American Books is a subsidiary of Scientific American, Inc.
Distributed by W. H. Freeman and Company, 41 Madison Avenue,
New York, New York 10010 and 20 Beaumont Street,
Oxford OX1 2NQ England

Third printing 1996, HC

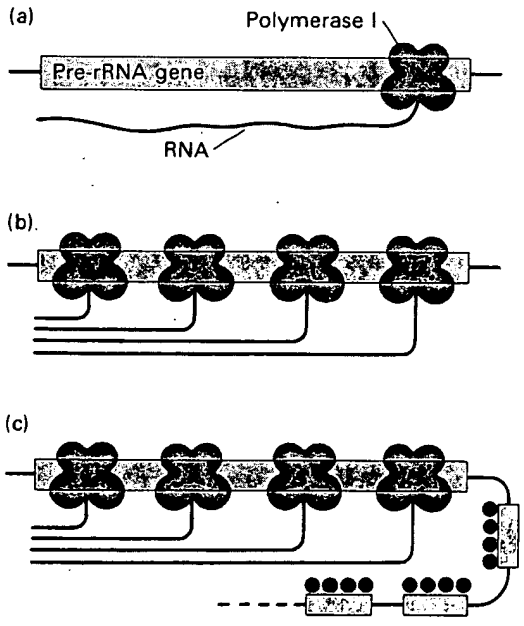
Present-day gibbons survive perfectly well with one adult β-like globin gene.

Pseudogenes have been identified in various other gene families, including the tubulin and actin gene families. In addition to the complete but nonfunctional gene copies that constitute pseudogenes, partial copies of some genes have been identified. For example, sequences corresponding to fragments of the 5′ and 3′ ends of the tubulin genes are quite common in human DNA. These presumably arose by unequal crossovers within the tubulin genes, rather than in adjacent regions as diagrammed in Figure 9-6. As discussed in a later section, other nonfunctional gene copies can arise by reverse transcription of mRNA into cDNA and integration of this intron-less DNA into a chromosome.

rRNAs, tRNAs, and Histones Are Encoded by Tandemly Repeated Genes

The genes for the rRNAs, each type of tRNA, and one family of proteins, the histones, which package nuclear DNA into chromatin, occur in invertebrates and some vertebrates as *tandemly repeated arrays*. These are distinguished from the duplicated genes of gene families in that the multiple tandemly repeated genes encode identical or nearly identical proteins or functional RNAs. Most often copies of a sequence appear one after the other, in a head-to-tail fashion, over a long stretch of DNA. Within a tandem array of rRNA or tRNA genes, each copy is exactly, or almost exactly, like all the others. Although the transcribed portions of rRNA genes are the same in a given individual, the nontranscribed spacer regions between the transcribed regions can vary. Arrays of tandemly repeated histone DNA are somewhat more complex; however, each histone gene, too, has multiple identical copies.

The tandemly repeated rRNA, tRNA, and histone genes are needed to meet the great cellular demand for their transcripts. Most of the RNA in a cell consists of rRNA and tRNA. Assuming RNA polymerase molecules move at a fixed speed, there must be a limit to the number of RNA copies that transcription of a single gene can provide during one cell generation, even if it is fully loaded with polymerase molecules. If more RNA is required than can be transcribed from one gene, multiple copies of the gene are necessary, as illustrated in Figure 9-7 for the synthesis of pre-RNA, which is processed into 18S, 5.8S, and



Copies of gene	Number of polymerases per gene	Yield of pre-rRNA per 24 h
1	1	288
1	≈250	≈70,000
100	≈250	≈7,000,000

▲ FIGURE 9-7 Effect of copy number and loading with RNA polymerase I on rate of synthesis of pre-rRNA in human cells. Genes encoding pre-rRNAs, which are processed into the 18S, 5.8S and 28S rRNAs, are transcribed by the enzyme RNA polymerase I. Transcription of the pre-rRNA gene by a single molecule of RNA polymerase I takes about 5 min. (a) If a cell contained one copy of the pre-rRNA gene, which was transcribed by one polymerase at a time, it could produce a maximum of 288 copies per 24 h. (b) The yield of pre-rRNA from a single copy of the pre-rRNA gene would increase substantially if the gene was maximally loaded with ≈250 polymerase molecules. (c) The highest rate of pre-rRNA synthesis is possible when a cell contains multiple copies of the pre-rRNA and these are transcribed by many polymerase molecules at one time. (Duplicate genes are indicated by small blue rectangles and polymerases by red circles). In order to generate enough rRNA to divide every 24 h, human embryonic cells must have at least 100 copies of the rRNA gene and these must be near maximally loaded with RNA polymerase I.

28S rRNA. For example, during early embryonic development in humans, many embryonic cells have a doubling time of ≈24 h and contain 5–10 million ribosomes. To produce enough rRNA to form this many ribosomes, an embryonic human cell needs at least 100 copies of the pre-rRNA gene, and most of these must be close to maximally active for the cell to divide every 24 h (see Figure 9-7c). The importance of repeated rRNA genes is illustrated by *Drosophila* mutants called "bobbed" (because they have stubby wings), which lack a full complement of the tandemly repeated rRNA genes. A bobbed mutation that reduces the number of rRNA genes to less than ≈50 is a recessive lethal mutation.

Genes encoding many functional RNAs other than mRNA exist in multiple copies in eukaryotic cells (Table 9-3). All species, including yeasts, contain 100 or more copies of the genes encoding 5S rRNA and pre-rRNA. More than 20,000 copies of the 5S rRNA gene are present in frogs. The copy number for individual tRNA genes ranges from 10 to 100. The multiple copies of all the rRNA genes occur in tandem arrays.

TABLE 9-3 Copy Number of Tandemly Repeated Genes Encoding Structural RNAs in Several Eukaryotes*

Species	Number of Copies		
	Pre-rRNA Gene	5S-rRNA Gene	tRNA Genes†
Saccharomyces cerevisiae	140	140	250
Dictyostelium discoideum	180	180	?
Tetrahymena pyriformis			
Micronucleus‡	1	300	800
Macronucleus	200	300	800
Drosophila melanogaster			
X chromosome	250	165	860
Y chromosome	150	165	860
Xenopus laevis	450	24,000	1150
Human	≈250	2000	1300

* The copy numbers in this table were estimated by hybridizing saturating amounts of labeled RNA to DNA.
† The tRNA numbers include all tRNA sites and therefore represent more than 50 different tRNA genes in some organisms. Copy numbers for individual tRNAs range from 10–100.
‡ The micronucleus is inactive in synthesis of pre-rRNA.
SOURCE: B. Lewin, 1980, *Gene Expression*, Vol. 2, Wiley, p. 876.

➢ *Discovery of Repetitious DNA Fractions*

Besides the duplicated protein-coding genes and the tandemly repeated genes encoding rRNAs, tRNAs, and histones discussed in the previous section, eukaryotic cells contain multiple copies of other DNA sequences in the genome. These are generally referred to as *repetitious DNA* (see Table 9-1). Some of these sequences are quite short and occur as *tandem* repeats; others are much longer and are *interspersed* at many places in the genome. The existence of these repeated sequences was first recognized in reassociation experiments in which denatured eukaryotic DNA was observed to renature nonuniformly; that is, some of it reassociated much more rapidly than the bulk of cellular DNA. Here we briefly review the experimental evidence that led to discovery of the two major classes of repetitious DNA; later, we discuss each class in more detail.

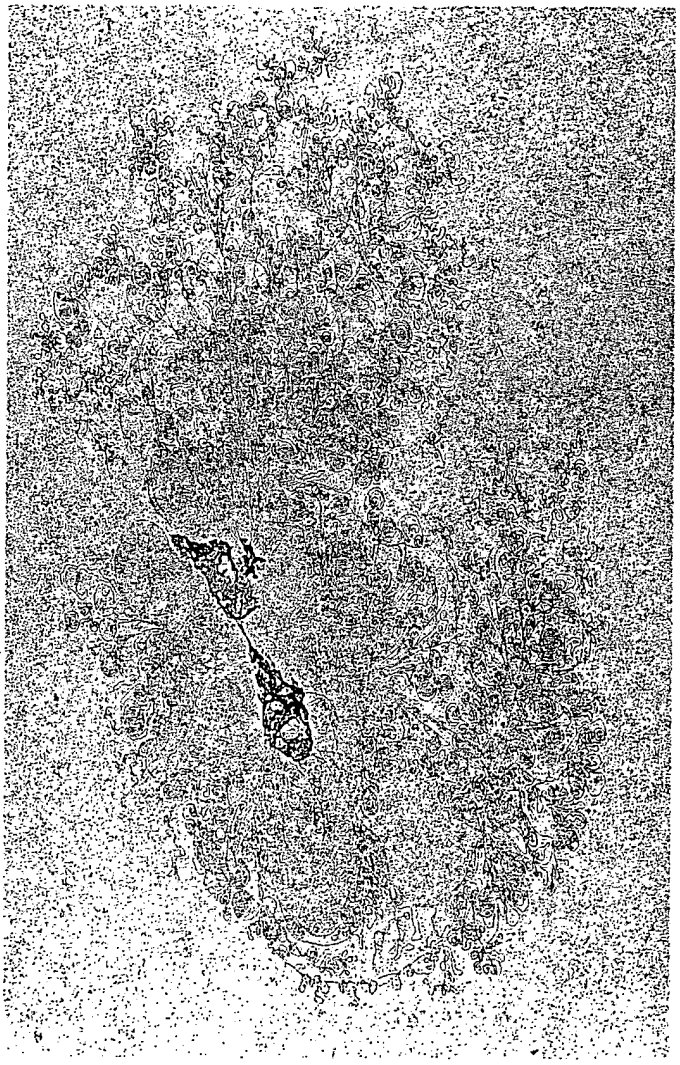
Repeated DNA Reassociates More Rapidly Than Nonrepeated DNA

Suppose that the total DNA of an organism is broken into fragments with an average length of about 1000 base pairs. The DNA is then melted into single strands and placed under conditions that allow strand reassociation to occur (e.g., a favorable ion concentration and a favorable temperature). All the DNA fragments would re-form duplexes at about the same speed if none contained sequences that were repeated in the genome. However, a segment containing a sequence repeated many times in the genome would find a complementary partner more quickly than a segment with a sequence that occurs only once per haploid genome, because the repeated sequence would be present at a much higher concentration. Consequently the repeated sequence would reassociate faster than the fragment of unique sequence. For this reason, the DNA encoding pre-rRNA and that encoding 5S rRNA reassociate faster than does nonrepeated DNA.

The parameters that affect the degree to which single-stranded DNA reassociates are its initial concentration and the time allowed for the reaction. The $C_o t$ of a reaction is the product of the concentration of the DNA measured in moles of nucleotide per liter C_o and the reaction time t in seconds. A convenient term for comparing the reassociation rates of different DNA fractions is the $C_o t_{1/2}$ value—the $C_o t$ at which one-half of a given fraction renatures. The lower the value of $C_o t_{1/2}$, the higher the reassociation rate. By comparing the $C_o t_{1/2}$ value of any particular DNA fraction with that of a "standard" nucleic acid (e.g., a viral or bacterial DNA of known length, both of which have either no or very few repetitive sequences), the approximate frequency of repeats within the fraction of interest can be determined.

somal DNA, causing it to fold into a more compact structure. The most abundant of these proteins, H-NS, is a dimer of a 15.6-kDa polypeptide. H-NS binds DNA tightly and compacts it considerably, as measured by an increased rate of sedimentation during centrifugation and decreased viscosity. There are about 20,000 H-NS molecules per cell, enough for one H-NS dimer per ≈400 base pairs of DNA.

Finally, *E. coli* chromosomal DNA is tightly supercoiled—that is, twisted upon itself like the circular SV40 DNA shown in Figure 4-14. As discussed in Chapter 10, an *E. coli* enzyme called DNA gyrase can introduce negative supercoils into DNA. Supercoiling contributes to the compaction necessary to fit chromosomal DNA into the bacterial cell. Figure 9-45 is an electron micrograph of an isolated, highly supercoiled *E. coli* chromosome attached to a fragment of cell membrane.

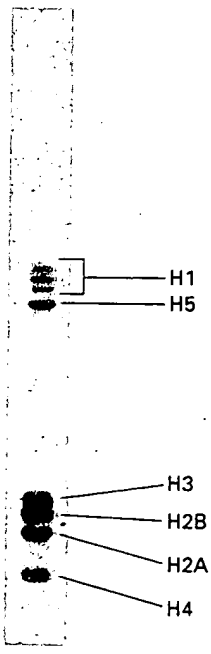


▲ FIGURE 9-45 Electron micrograph of an isolated folded *E. coli* chromosome. The highly supercoiled DNA is attached to a fragment of the cell membrane appearing as the most darkly staining material in the micrograph. Although the highly supercoiled nature of the *E. coli* chromosome is illustrated by this electron micrograph, the chromosome actually decondensed considerably during isolation. Within the cell, the chromosome has a diameter of <1 μm. [From H. Delius and A. Worcel, 1974, *J. Mol. Biol.* **82**:107.]

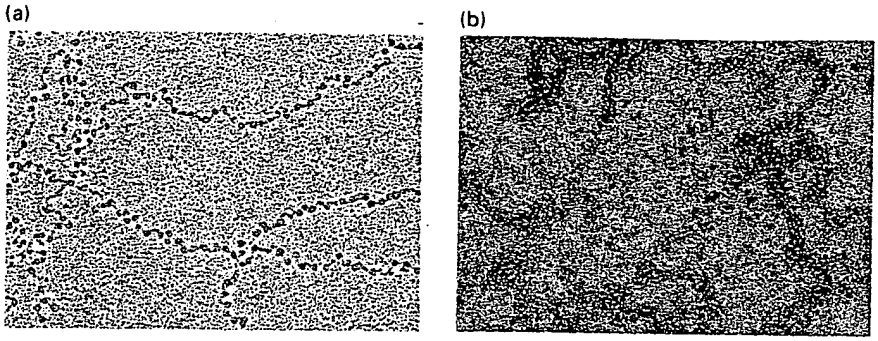
Eukaryotic Nuclear DNA Associates with Highly Conserved Histone Proteins to Form Chromatin

The problem of compacting cellular DNA is also significant for eukaryotic cells. When the DNA from eukaryotic nuclei is isolated in isotonic buffers (i.e., buffers with the same salt concentration found in cells, ≈0.15 M KCl), it is found associated with an equal mass of protein in a highly compacted complex called *chromatin*. The general structure of chromatin has been found to be remarkably similar in all eukaryotic cells.

The most abundant proteins associated with eukaryotic DNA are *histones*, a family of basic proteins found in all eukaryotic nuclei. The five major types of histone proteins—termed H1, H2A, H2B, H3, and H4—are easily separated by gel electrophoresis (Figure 9-46). The histone proteins are rich in basic amino acids, which contact negatively charged phosphate groups in DNA. In a fraction of the histone proteins of most cells, some of the basic amino acid side chains are modified by post-translational addition of methyl, acetyl (CH_3CO-), or phosphate groups, neutralizing the positive charge of the side chain or converting it to a negative charge.



◀ FIGURE 9-46 Gel electrophoretic separation of histone proteins extracted from chicken blood cells. The major histone species—H2A, H2B, H3, and H4—are present in about equal amount. The other major histones are H1, which is found in white blood cells and most other vertebrate cells, and H5, which is similar to H1 and replaces it in the red blood cells of birds. The separation of H1 into three bands results from differences in the extent of phosphorylation of residues in the protein. [Courtesy of V. Allfrey.]



▲ FIGURE 9-47 Electron micrographs of extracted chromatin in extended and condensed forms. (a) Chromatin isolated in low ionic strength buffer has an extended "beads-on-a-string" appearance. The "beads" are nucleosomes (10-nm diameter) and the "string" is connecting DNA. (b) Chromatin isolated in buffer with a physiologic ionic strength (0.15 M KCl) appears as a condensed fiber 30 nm in diameter. [Left micrograph courtesy of S. McKnight and O. Miller, Jr.; right micrograph courtesy of B. Hamkalo and J. B. Rattner.]

The amino acid sequences of four histones (H2A, H2B, H3, and H4) from a wide variety of organisms are remarkably similar among distantly related species. For example, the sequences of histone H3 from sea urchin tissue and of H3 from calf thymus are identical except for a single amino acid, and only four amino acids are different in H3 from the garden pea and that from calf thymus. Minor histone variants encoded by genes that differ from the highly conserved major types also exist, particularly in vertebrates.

The amino acid sequence of H1 varies more from organism to organism than do the sequences of the other major histones. In certain tissues, H1 is replaced by special histones. For example, in the nucleated red blood cells of birds, a histone termed H5 is present instead of H1 (see Figure 9-46). Despite minor variations, the similarity in the amino acid sequences of the major histones among all eukaryotes is most impressive.

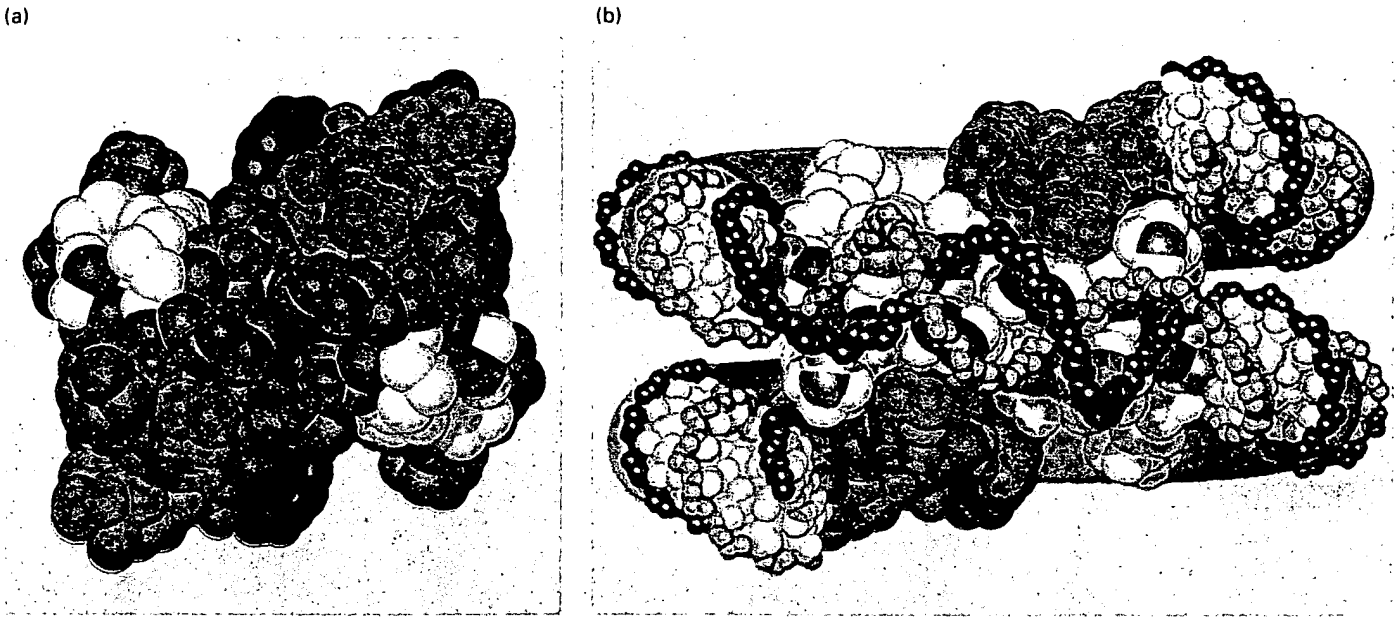
Chromatin Exists in Extended and Condensed Forms

When chromatin is extracted from nuclei and examined in the electron microscope, its appearance depends on the salt concentration to which it is exposed. At low salt concentration, isolated chromatin resembles "beads on a string" (Figure 9-47a). In this extended form, the string is a thin filament of DNA connecting the beadlike structures termed *nucleosomes*. Composed of DNA and histones, nucleosomes are about 10 nm in diameter and are the primary structural units of chromatin. If chromatin is isolated at physiologic salt concentration (≈0.15 M KCl), it assumes a more condensed fiber-like form 30 nm in diameter (Figure 9-47b).

Structure of Nucleosomes Individual nucleosomes can be isolated by nuclease digestion of extracted chromatin, because the DNA component of nucleosomes is much less susceptible to digestion than is the linker DNA connecting nucleosomes. Partial nuclease treatment first releases groups of nucleosomes by digestion of the linker DNA between some of the nucleosomes. More extensive digestion produces nucleosome tetramers, trimers, and dimers. Eventually, nuclease treatment digests all the DNA between individual nucleosomes, so that all the nucleosomes are released. The DNA content of a single nucleosome plus the DNA linking neighboring nucleosomes varies between 160 and 200 base pairs in different organisms. After digestion of all the linker DNA, nucleosomes from all eukaryotes contain close to 146 base pairs of DNA.

A nucleosome is composed of a protein core with DNA wound around its surface like thread around a spool. The core is an octamer containing two copies each of histones H2A, H2B, H3, and H4. X-ray crystallography has shown that the octameric histone core is disk shaped (Figure 9-48). About 146 base pairs of DNA are wrapped slightly less than two turns around the core to form the nucleosome.

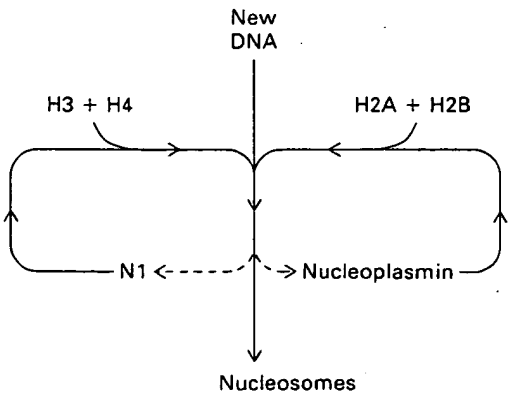
Assembly of Nucleosomes Newly replicated DNA quickly associates with already formed histone octamers. A model of nucleosome assembly has been proposed based on studies with rapidly dividing fertilized frog oocytes. Analysis of protein complexes isolated from early frog embryos revealed two acidic nonhistone proteins associated with the basic histone proteins that were not assembled into nucleosomes. One of these nonhistone proteins, called *nucleoplasmin,* was found bound to H2A and H2B; the other, called *N1 protein,* to H3 and H4. When partially purified preparations of these two complexes were mixed in the presence of DNA, nucleosomes were formed with release of free nucleoplasmin and N1 (Figure 9-49). Proteins resembling nucleoplasmin and N1 have been identified in other cell types. Thus, the proposed pathway of nucleosome assembly may operate in most cells.



▲ FIGURE 9-48 Structure of the histone octamer and the nucleosome. (a) Model of octameric histone core based on a 3.1 Å resolution structure determined by x-ray crystallography. The histone core contains two copies each of H2A (light blue), H2B (dark blue), H3 (green), and H4 (white). The spheres represent amino acid residues, not atoms. The positively charged arginine and lysine residues are red. The amino termini of the histone proteins are not visualized by x-ray crystallography, but they are thought to extend outward from the top and bottom of this view of the histone octameric core. (b) Model of the nucleosome in which the octameric core is represented by one centrally located $(H3/H4)_2$ tetramer (white) flanked by two H2A/H2B dimers (blue); 146 base pairs of DNA (gray) are wrapped 1.75 supercoil turns around the histone core. In the central area of the picture, the DNA bases (light gray) have been stripped away and the path of the phosphodiester backbones is represented by medium and dark gray spheres; these are "undersized" in order to visualize the matching of the pattern of the positively charged residues (red spheres) on the surface of the histone octamer with the negatively charged DNA backbone. The α-helix dipoles are indicated by orange. [See G. Arents and E. N. Moudrianakis, 1993, *Proc. Nat'l. Acad. Sci.* **90**:10489; courtesy of E. N. Moudrianakis.]

Solenoid Structure of Condensed Chromatin In its condensed form, chromatin appears as fibers ≈30 nm in diameter (see Figure 9-47b). A model for the structure of these thick fibers is shown in Figure 9-50. In this model, nucleosomes are packed into a spiral or solenoid arrangement with six nucleosomes per turn. A fifth histone, H1, is bound to the DNA on the inside of the solenoid, with one H1 molecule associated with each nucleosome. The unit of one nucleosome plus one bound H1 is referred to as a *chromatosome*. Under various conditions, condensed chromatin is further folded into giant supercoiled loops.

As noted earlier, when chromatin is extracted at the physiologic salt concentration, condensed 30-nm solenoid fibers are obtained. However, when extraction is done at a low salt concentration, H1 is released, yielding the extended beads-on-a-string form. Thus, depending on the extraction conditions, two forms of chromatin can be observed experimentally in vitro. As discussed in the next section, the chromatin in chromosomal regions that are not being transcribed exists predominantly in the condensed form, whereas that in regions being transcribed probably assumes the extended form.



◀ FIGURE 9-49 Proposed pathway of nucleosome assembly in frog eggs. Both N1 and nucleoplasmin are acidic proteins that have been shown to associate with histones as indicated. [Adapted from S. M. Dilworth et al., 1987, *Cell* **51**:1009.]

The Peptides *Volume 5*

EXHIBIT C

THE PEPTIDES
Analysis, Synthesis, Biology

Treatise Editors
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The Peptides

Analysis, Synthesis, Biology

VOLUME 5 Special Methods in Peptide Synthesis, Part B

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Chemical Research Department
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Nutley, New Jersey

1983

ACADEMIC PRESS
A Subsidiary of Harcourt Brace Jovanovich, Publishers
New York London Paris San Diego
San Francisco São Paulo Sydney Tokyo Toronto

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

Library of Congress Cataloging in Publication Data

(Revised for volume 5)
Main entry under title:

The Peptides.

Includes bibliographies and indexes.
Contents: v. 1. Major methods of peptide bond formation. -- v. 2. Special methods in peptide synthesis -- [etc.] -- v. 5. Special methods in peptide synthesis, part B.
1. Peptides. I. Gross, Erhard. II. Meienhofer, Johannes. [DNLM: 1. Peptides. QU 68 P424 1979]
QP552.P4P47 574.19'245 78-31958
ISBN 0-12-304205-4 (v.5) (San Diego).

PRINTED IN THE UNITED STATES OF AMERICA

83 84 85 86 9 8 7 6 5 4 3 2 1

ERHARD GROSS, 1928–1981

Erhard Gross, the conceptual originator of this treatise, died in a traffic accident in Germany on September 12, 1981. In an instant, Gross passed away in the most productive period of his scientific work.

He had great visions about the importance of collecting any and all information on peptides and presenting it in a concise and comprehensive form to the scientific community. Many different approaches were considered, including a translation of the monumental Houben-Weyl by Erich Wünsch (Thieme, Stuttgart, 1974). Eventually, the present open-ended treatise, *The Peptides: Analysis, Synthesis, Biology*, appeared to provide the best way to generate the desired timely information transfer. Once this was decided, Gross spent countless hours on correspondence and telephone conversations in efforts to enlist authors of international reputation. We shall forever miss his inspiration and tireless pursuit of excellence in this venture.

Erhard Gross was not a novice in producing books on peptides. In the 1960s, when modern methods of peptide synthesis had undergone a dramatic expansion, Gross undertook the difficult task of translating the two volumes, *The Peptides* (E. Schröder and K. Lübke) from German into English (Academic Press, 1965/1966). Undoubtedly, the impact of these books on the explosive development of all areas of peptide research will be remembered by many colleagues. Without the English translation, progress would almost certainly have been much slower.

Erhard Gross was born in Wenings, near Frankurt am Main. He studied chemistry at the Universities of Mainz and Frankfurt and received his doctoral degree in 1958. His thesis on the synthesis of a bicyclic model peptide of the mushroom toxin phalloidin was carried out in the laboratory of Professor Theodor Wieland. Gross came to the United States in 1958. He worked for many years with Professor Bernhard Witkop at the

Chapter 6

Unusual Amino Acids in Peptide Synthesis

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New Jersey

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I. INTRODUCTION

In a 1972 review article, Josef Rudinger concluded that the design of peptide hormone analogs would prove more fruitful if chemists were to be "less reluctant . . . to abandon the facile use of ready-made bricks, the protein-constituent amino acids, and to undertake sometimes quite intricate syntheses to meet the designs which will best answer a given purpose." It is apparent that this view has since gained increasing acceptance within the peptide community; it is the authors' purpose in writing this review to assess what has actually been done to date in the development and use of non-standard building blocks in peptides and to compile a reference list of unusual amino acids that have been or might be used in peptide synthesis.

We have not attempted to be exhaustive in our coverage but rather have presented selected examples illustrating the various motivations and strategies behind the use of unusual amino acids in peptides. We apologize to the authors of many important articles which, because of space and time limitations, are mentioned very briefly or cited only as references. We also warn the reader that this review was implicitly written from the standpoint of peptide hormone-based medicinal chemistry. Specialized topics such as the synthesis of peptide antibiotics containing unusual hydroxyamino acids have not been included.

A. Literature Sources

The literature on unusual amino acids prior to 1960 has been covered by Greenstein and Winitz (1961); the authors also call the reader's attention to a number of review articles with a natural product emphasis (Meister, 1965; Fowden, 1964, 1970; Fowden *et al.*, 1979; Vickery, 1972; Lea, 1978). As our sources, we have relied heavily on the annual *Specialist Periodical Reports on Amino Acids, Peptides, and Proteins* (Chemical Society), supplemented by the *MTP International Review of Science—Organic Chemistry* Series, the compendia of Pettit (1970, 1973, 1975, 1976), and a review by Mooz (1974), along with standard literature search sources. None of these sources address the present subject in a comprehensive way. It is the authors' hope that this chapter will provide peptide chemists with an awareness of existing capabilities for structural variation in peptides and open the door to strategies of drug design previously employed only in more traditional areas of medicinal chemistry.

B. Types of Structural Variants of Peptides

Departures from the sole use of the coded amino acids in peptide structures may involve relatively straightforward procedures such as modification (acylation, alkylation, etc.) of side-chain functional groups of coded amino acids, acylation of the NH_2-terminus with simple carboxylic acids or attachment of amines to the COOH-terminus, and replacement of one or more amino acids in a chain with a noncoded counterpart. This category, being for the most part available within the confines of standard procedures for peptide synthesis (including solid-phase techniques), is perhaps the most straightforward means by which peptide chemists can expand their repertoire of available structural variation and therefore provides the main focus of this review.

A number of more radical measures are also available to chemists. These include the use of α-azaamino (Dutta and Morley, 1975; Powers and Gupton, 1977) and α-dehydroamino (Chapter 5, this volume) acids, which require special treatment owing to their chemical constitution. The synthesis of retro-inverso sequences (Goodman and Chorev, 1981), which involves the use of malonic acid derivatives and *gem*-diamines, also requires unusual procedures. Replacement of the peptide linkage at a particular position with some more or less isosteric but chemically distinct functionality (esters, ethers, etc.), may also require some involved synthetic transformations. Finally, major surgery of the sort so dramatically demonstrated by the Merck group in the case of somatostatin, in which a large fragment was replaced with a simple linkage that fulfilled the same role in maintaining the active conformation (Veber *et al.*, 1979; Veber, 1981), provides a striking recent example.

C. Scope of This Review

The table of amino acids in the Appendix includes only α-amino acids, and (with a few exceptions) only those for which syntheses have been reported in the literature. Amino acids cited by Greenstein and Winitz (1961) are

referenced to that review and not to the original work or (with a few exceptions) to any more recent works. We have further excluded certain types of α-amino acids which, in our opinion, would not have substantially increased the value of the chapter but would have added a great deal of bulk; see the introduction to the Appendix for details. In the text of the present chapter, the authors have occasionally overstepped these boundaries in the interests of historical and logical continuity; in addition, we have incorporated a brief overview of dipeptide isosteres, which can often be treated as simple amino acids for the purposes of peptide synthesis and represent an especially exciting modern development. We have attempted in the text to give a comprehensive overview of the various applications that call for unusual amino acids, and have chosen examples for discussion that illuminate these applications. We have not attempted to discuss all noteworthy amino acids, and many important pieces of work are omitted or only briefly mentioned in the text. We have, however, attempted to give complete, up-to-date reviews of those applications that are covered. Aside from a few more recent works, the literature through 1981 is covered.

D. Reasons for Using Unusual Amino Acids

Traditional peptide structure–activity studies employing coded amino acids have had as their goal, and have often realized, some of the potential benefits outlined in Table I. However, many previously unavailable possibilities are opened up when such studies embrace the incorporation of groups sterically and functionally different from those present in the coded amino acids. Techniques such as affinity labeling, studies with spectroscopic probes, and novel chemical modifications are now possible through the incorporation of appropriate functional groups. Furthermore, the transport and metabolism of peptide analogs can be affected much more dramatically by departing from the sole use of coded amino acids, and the much wider range of available molecular shapes and chemical functionality enhances the likelihood of further optimization of receptor binding and of other pharmacological properties. These capabilities, and the impressive successes they have made possible, should serve to reassure chemists who fear that recombinant DNA technology and its inevitable success in the production of natural peptides will render their services obsolete.

It has been pointed out by Rudinger (1972) and others that structure–activity data are more easily interpreted if structural changes are made isosteric or "isofunctional" whenever possible. The use of unusual amino acids makes newly possible many such substitutions; indeed many of the unusual amino acids reviewed here seem to have been developed just for

Table I. Benefits To Be Gained by Using Unusual Amino Acids and Other Unnatural Structural Variations of Peptides

Improved drug–receptor interactions
Study of strength and nature of binding (including selecting out certain types of activity)
Effects on fit
Steric compatibility of active conformation with receptor site
Enhancement of active conformation relative to others
Effects on strength of chemical interactions
Electrostatic polar interactions
Hydrophobic interactions
Irreversible binding
Affinity labeling of allosteric binding sites
Prolonged pharmacological activity due to irreversible receptor binding
Improved pharmacokinetic properties
Interactions with peptide-processing enzymes
Resistance to enzymatic degradation
Pharmacological effects resulting from inhibition of peptide-processing enzymes
Effects on drug delivery and excretion
Effects on solubility, mobility, tissue specificity
Slow chemical release of active species
Development of tools for study of peptide chemistry and biology
Spectroscopic probes of peptide conformations and interactions
Affinity labeling as probe for enzymes and receptors
Radiolabeled peptides for anatomical and pharmacological studies
Facilitated chemical synthesis of peptides
Improved stability and physical properties of product
Structural variation that allows retention of activity in smaller, simpler molecules
Easy modification of side-chain functionality following incorporation into a peptide chain
Unusual amino acid required as component of a natural product (and needed for any of the above reasons)

such purposes. Although analogs containing them might not themselves show dramatically improved activity, they can impart order to the structure–activity data and ultimately lead to the rational formulation of analogs possessing the sought characteristics.

Ideally, an article such as this would provide its readers with easily applied information as to how a given unusual amino acid may be expected to function in affecting the activity of an analog. The authors hesitate to attempt this, as available activity data often reflect structural changes in ways that are not obvious. A change in structure may function differently in different situations—in receptor binding or even at the level of gene expression from which the distribution of enzymes and receptors themselves may be affected. A statement such as, "Pyridylalanines function as six-ring analogs of histidine," although simplifying matters neatly, may not only be untrue but is likely to cause readers to ignore other possible analogies. In

many cases, however, it may be clear that the investigator's *intent* was to use, for example, pyridylalanines as functional analogs of histidine; this review will attempt to limit itself to these more harmless interpretations.

II. ISOFUNCTIONAL AND HOMOFUNCTIONAL REPLACEMENT

Perhaps the most subtle way to vary the structure of a peptide hormone is to change only its steric properties and leave its functional groups intact and in the same approximate relative geometry. Although in a few cases it is possible to do this by substituting one coded amino acid for another (e.g., threonine for serine, aspartic acid for glutamic acid), most such modifications require the introduction of a noncoded amino acid. Simple homologs, that is, structures that contain greater or lesser numbers of methylene groups in the side chain than the natural amino acid or are otherwise functionally similar, are known for most amino acids. Much of the early work with noncoded amino acids involved substitutions of this type, some of which have seen extensive use in peptides. In general, changing the steric properties of a peptide hormone does not result in a significant improvement of potency and in many cases lowers potency severely. Its most useful application is in cases where the spectrum of physiological activity is altered by modification (i.e., suppression of one type of activity while preserving another).

A. Fatty Amino Acids

The use of unnatural fatty (hydrocarbon) amino acids as steric probes of the receptor site was pioneered by Rudinger and co-workers (Eisler *et al.*, 1966) in their studies on oxytocin analogs; they found, as have many other investigators, that natural fatty and aromatic residues can often be replaced by unnatural analogs without sacrificing biological activity. In some cases, stability to enzymatic cleavage can be introduced in this way without sacrificing biological activity, as in the case of [adamantylalanine^5]-enkephalin analogs (Do and Schwyzer, 1981). The reader is cautioned that certain fatty amino acids, notably *tert*-alkylglycines, may be expected to pose problems in synthesis as a result of the steric bulk of the side chain; for example, difficulty was encountered in coupling active esters of protected *tert*-leucine (β-methylvaline), whereas acylation of the amino acid proceeded satisfactorily (Pospíšek and Bláha, 1977).

Although substitutions of this type do not appear to afford significant improvement in activity over that of the natural hormone, they can result in substantially modified activity. For example, Khosla *et al.* (1972) found striking antagonistic activity in angiotensin II analogs containing a cyclohexylalanine residue in place of phenylalanine. This replacement is not strictly isofunctional because of the electronic properties of the aromatic ring in phenylalanine. In fact, such replacements have been used as probes of biological requirements for aromaticity (Fletcher and Young, 1972), and a similar use has been described for partially saturated phenylalanines (Ressler *et al.*, 1979). Differences in activity are sufficiently minor as to be attributable to the steric nonequivalence of the hydrogenated phenylalanine derivatives relative to phenylalanine. To the authors' knowledge, there are no cases where a functional requirement for aromaticity per se has been demonstrated. The steric similarity between cyclohexylalanine and phenylalanine has been used in polyamino acid CD studies where the interference of the chromophoric side chain causes problems (Peggion *et al.*, 1970).

B. Aromatic Series

Replacement of an aromatic residue with a nonnatural counterpart produces a common type of structural variant. Abrupt changes in functionality (e.g., replacing phenylalanine with tyrosine) often result in a loss of activity; however, more nearly isofunctional replacements often result in preserved or even enhanced activity. A series of substituted phenylalanines, including alkyl and alkoxy, were employed as replacements at position 2 of oxytocin, and the bulkier groups were found to impart a strong antagonist activity to the analogs (Rudinger, 1972). Typically, replacement of phenylalanine with sterically similar substituted aromatic residues does not grossly affect the activity; for example, Morley and co-workers (Morley, 1968; Gregory *et al.*, 1968) have found that para substitution of the phenylalanine residue in gastrin tetrapeptide with various types of groups (methyl, methoxy, nitro, fluoro) can be done without sacrificing activity. 4-Fluorophenylalanine (Nicolaides *et al.*, 1963) is very nearly isosteric with phenylalanine and has found considerable application in adjusting hormonal activity. 4-Nitrophenylalanine has also been used extensively; enhanced activity of enkephalin analogs containing this amino acid appears to stem from the electron-poor character of the aromatic ring (Fauchère and Schiller, 1981; Schwyzer, 1980). 3-Tyrosine is another interesting isofunctional variant that has been used (Bernardi *et al.*, 1966). An unusual phenylalanine homolog that has found considerable application is 3-(2-thienyl)alanine (du Vigneaud *et al.*, 1945; Dunn and Stewart, 1971).

C. Large Aryl Side Chains

Larger or fused-ring aromatic amino acids have been used as replacements for both phenylalanine and tryptophan residues. The naphthylalanines and various other tryptophan isologs employed by Yabe *et al.* (1976) generally provide analogs with reduced activity. Tesser and co-workers have used pentamethylphenylalanine as a replacement for tryptophan in several types of hormone analogs, including those of α-melanotropin (α-MSH), which exhibit useful potency (Van Nispen *et al.*, 1977b); they have found that more nearly isosteric but less electron-rich tryptophan isologs give less active peptides and have concluded that strong π-donor properties of tryptophan isologs are more important than steric equivalence in preserving hormonal activity. This is apparently not always the case, as seen in studies by Rajh *et al.* (1980). Extensive studies on the replacement of Trp^6 in luliberin (LHRH) analogs have been carried out in a search for antifertility agents. A series of bulky carbocyclic (Nestor *et al.*, 1981, 1982a) and heteroaromatic (Nestor *et al.*, 1982b) amino acids, some representing considerable steric and electronic deviation from tryptophan, provided analogs with potent superagonist activity.

Other large aromatic amino acids of potential interest are styrylphenylalanine (Jones and Wright, 1971), with a photoisomerizable double bond, and anthracene derivatives of possible use in photophysical studies (Ben-Ishai *et al.*, 1978; Nestor *et al.*, 1982a; Schreiber and Lautsch, 1965).

D. Organometallic Amino Acids

Amino acids with side chains incorporating polyhedral carboranes and organometallic "sandwich" complexes have been proposed or utilized as homologs of phenylalanine or other bulky hydrophobic amino acids. Schwyzer and co-workers have, in the course of studies on unusual hydrophobic amino acids, introduced 3-*o*-carboranylalanine, which is claimed to occupy a space nearly equal to that swept by a 180° rotation of the phenylalanine aryl group. Their studies show that analogs containing this unusual group can exhibit enhanced activity in some cases (Fauchère *et al.*, 1979) and, interestingly, that this may be a result more of the electron deficiency of the carborane nucleus than its steric bulk (Schwyzer, 1980; Fauchère and Schiller, 1981).

Greater deviations in shape from that of phenylalanine are seen in amino acids with organometallic π-complexes incorporated into their side chains. Ferrocenylalanine has been incorporated into peptide structures and exhibits the interesting ability to undergo a reversible one-electron oxidation

to provide a cationic side chain that imparts water solubility and a deep-green color to derivatives (Cuingnet *et al.*, 1980; Pospíšek *et al.*, 1980). Also of interest are amino acids with cyclobutadiene, cyclopentadienyl (Brunet *et al.*, 1981a), and benzene (Brunet *et al.*, 1981b) metal carbonyl complexes. These are of interest for their unusual steric properties and for their possible use in photoaffinity labeling, which results from the known ability of various groups (e.g., amines) to replace CO in such complexes under photolysis.

III. ISOSTERIC AND HOMOSTERIC REPLACEMENT

The role of functional group interactions in allosteric binding of peptide hormones is at least equal in importance to steric fit and is undoubtedly the source of most of the specificity characteristic of these interactions. Although hormone–receptor binding is optimized both sterically and functionally by evolution within the limitations of the coded amino acids, it is in principle possible, by employing functional groups other than those in the coded amino acids, to create interactions significantly stronger than those present in the natural system; for this reason it seems that functional variants of peptides are more likely than steric variants to provide analogs with enhanced or modified activity. Below are outlined some of the more extensively studied functional variants of amino acids.

A. Histidine Isosteres

An early example of isosteric substitution in investigating the effects of functional changes is the use of histidine isologs in which the imidazole ring is replaced with a pyrazole nucleus (Hofmann *et al.*, 1968). This involves a change in the arrangement of nitrogen atoms relative to those in histidine, as well as a significant lowering of their basicity; steric changes are insignificant. It was found that the catalytic activity of ribonuclease S was entirely lost when the enzyme was reconstituted using an analog of S-peptide containing a β-(3-pyrazolyl)alanine residue in place of the catalytically functional histidine (Hofmann *et al.*, 1970). In contrast to this the activity of a variety of peptide hormones was retained (although it was often significantly weakened) in analogs containing pyrazolylalanines in place of a histidine residue. It has been concluded from such studies that the basicity of the histidine residue per se is not a requisite for activity, however, it may in some cases contribute to the strength of binding. A fair variety of other histidine isosteres have been reported, but most of them have not yet been incorporated into peptides.

B. Pyridylalanines as Isologs of Phenylalanine and Histidine

Although a fair variety of derivatives of (2-, 3-, and 4-pyridyl)alanines have been reported, surprisingly little has been done to investigate their usefulness as components of peptides. Watanabe *et al.* (1968) report difficulties with coupling methods other than the dicyclohexylcarbodiimide (DCC) method in syntheses of β-(2-pyridyl)alanine-containing dipeptides. Veselova and Chaman (1973) successfully prepared a tripeptide from this amino acid. Especially attractive as isologs of tyrosine are the *N*-oxides of pyridylalanines (Sullivan *et al.*, 1968), although only their synthesis was reported.

C. Tetrazole-Containing Amino Acids

Following Morley's observation (1968) of the close steric and functional similarity between the tetrazole group and the carboxyl group, progress has been made in studying incorporation of the tetrazole nucleus at the sites of both side-chain and COOH-terminal carboxyl groups in peptides. Morley (1969) incorporated a tetrazole derivative of aspartic acid into an analog of gastrin tetrapeptide. Further studies reported by Grzonka's group involve synthesis of the γ-tetrazole derivative of glycine (Van Thach *et al.*, 1977, and references therein) and evidence from enzyme studies that the tetrazole–carboxyl similarity may not be as close as previously thought.

D. Functional Variants of Sulfur-Containing Amino Acids

Cysteine occurs in small peptides exclusively in the form of disulfide-bridged cystine, often serving to cyclize an otherwise linear peptide in order to stabilize an active conformation. Replacement of the cystine disulfide linkage with sterically similar linkages such as CH_2CH_2 and CH_2S was found not to lower hormonal activity in ground-breaking studies with oxytocin (Rudinger and Jošt, 1964; Jošt and Rudinger, 1967). This trend was subsequently confirmed for vasopressins and somatostatin. It was therefore not surprising that the selenium isolog of cysteine should function as a good substitute for this amino acid in such hormones, as a result of its tendency to form Se—Se and S—Se bonds which are chemically similar to disulfide linkages. Walter (1973) reported extensive structural and conformational studies of the selenium analog of oxytocin, in which the activity was comparable to that of the native hormone despite differing dihedral angles in the dichalcogenide linkage. Zdansky (1973) has reviewed the field of selenium-containing amino acids, including selenocysteine, selenomethionine, and various side-chain-methylated derivatives.

Functional variants of methionine are an especially interesting class of amino acids; unlike other amino acids, whose chemical functions are quite well understood, methionine remains something of a mystery with regard to the function of the sulfur atom. Although in some hormones, such as corticotropin, replacement of methionine with a sterically similar fatty amino acid such as norleucine can be made without sacrifice of activity, this is apparently not the case in gastrin tetrapeptide and others (reviewed by Rudinger, 1972); in general, *S*-ethylcysteine functions well as a substitute for methionine. The separate biological roles of Leu- and Met-enkephalins and their precursors are also striking when one considers their structural and functional similarity. It may be that the hydrocarbon-like steric and hydrophobic properties of methionine will not in themselves be sufficient to explain these differences.

IV. AMINO ACIDS EXERTING STRONG CONFORMATIONAL INFLUENCES

Any type of structural modification of a peptide might categorically be expected to influence the range of available conformations and/or the degree to which a given active conformation is preferred relative to others. This may in some cases be the primary means by which structural changes affect activity. Certain types of amino acid substitutions have been known for some time to exert powerful effects in this regard. As residues in a peptide chain, N-substituted amino acids including proline and its isologs function uniquely in that the amino nitrogen cannot serve as a hydrogen bond donor when incorporated into an amide linkage, which in turn lacks a marked preference for the trans conformation characteristic of the unsubstituted CONH linkage. Substitution of a proline residue in place of another (N-unsubstituted) amino acid of similar steric bulk (or vice versa) is therefore not as subtle a change as it might as first seem. α,α-Disubstituted amino acids also exert strong influences on conformation, directly by limiting the allowable values of the dihedral angles of bonds to the α-carbon. By the same token, glycine, being an α,α-unsubstituted amino acid, gives greater conformational freedom. From the standpoint of analog design, substitutions that preserve the gross conformational influences of the constituent amino acids in most cases prove to be the best strategy.

Because of space limitations, acyclic *N*-alkyl and acyclic α,α-disubstituted amino acids have been excluded from this review; the considerations above

give the present authors some hope that this omission will not seriously detract from the usefulness of the chapter.

A. Proline Isologs

A fair variety of substituted prolines are known, as there has been considerable interest in them as antimetabolites in collagen biosynthesis. Most of these variants have yet to be employed as components of peptides, with the notable exception of naturally occurring 4-hydroxyproline (Adams, 1977). One of the most popular replacements for proline is the 3,4-dehydro derivative; this amino acid was introduced by Robertson and Witkop (1962) and was claimed to be somewhat susceptible to racemization. Replacement of proline with this amino acid in bioactive peptides can, as a rule, be done without substantial loss of activity and in some cases enhances activity markedly, as in position 7 of oxytocin (Moore *et al.*, 1977a), in angiotensin-converting enzyme inhibitors (Fisher and Ryan, 1979; Natarajan *et al.*, 1979), and in angiotensin II (Moore, 1981). It also appears that this substitution can confer resistance to enzymatic degradation on a peptide (Fisher *et al.*, 1978). These effects are apparently mediated by the enhanced planarity imparted to the proline ring by the double bond, although the decreased steric bulk and enhanced polarizability of the π-cloud may contribute to the enhanced receptor affinity observed (Moore *et al.*, 1977a). Epoxidation of this amino acid provides another very interesting proline derivative which has not yet found application in peptide synthesis (Hudson *et al.*, 1975).

Thiazolidine-4-carboxylic acid and its 2-substituted derivatives are readily available as thioaminals from cysteine, and the unsubstituted version has found application as an isolog of proline in peptides, where it can provide enhanced activity and/or selectivity (Felix *et al.*, 1973; Rosamond and Ferger, 1976; Moore, 1981). This residue probably allows somewhat greater conformational freedom than proline itself. A variety of ring homologs of proline, with ring sizes varying from 3 to 15, are available, and some of them, notably azetidine-2-carboxylic acid and pipecolic acid, have been incorporated into peptide analogs in place of proline. This as a rule results in a significant loss of activity, at least in the neurohypophyseal hormone series (Barber *et al.*, 1979; Chaturvedi *et al.*, 1970; Neubert *et al.*, 1972) and verifies the crucial relationship between conformation and activity. Peptides incorporating the 6-ring and higher homologs will enjoy significantly enhanced conformational freedom; small-ring homologs will maintain rigidity, but bond angles differ. The latter still appear, on these grounds, to be promising as replacements for proline since few data to the contrary are presently available. By the same token, bicyclic prolines (Fujimoto *et al.*, 1971; Hughes *et al.*, 1980; Pirrung, 1980) appear promising as well.

A considerable number of benzo-fused cyclic imino acids are available, many of which are structurally related to biogenic amines. One noteworthy example is 1,2,3,4-tetrahydroquinoline-2-carboxylic acid, whose *N*-acyl or *N*-peptidyl derivatives can be caused to undergo dehydration–isomerization under mild conditions to give *O*-acylaminals potentially hydrolyzable to the peptide aldehyde (Zecchini and Paradisi, 1979).

B. 1-Aminocycloalkane-1-carboxylic Acids and Bicyclic Congeners

Although they do not correspond structurally to any of the coded amino acids, the sheer variety of cyclic α,α-disubstituted amino acids available in the literature warrants a close look by peptide chemists. Comparatively little has been done in the way of peptide chemistry involving these compounds, and the results have been disappointing [e.g., see angiotensin II analogs described by Park *et al.* (1974) and Hsieh *et al.* (1979)], as would be expected owing to conformational effects. A large number of interesting amino acids in this class, including various fused aromatic derivatives, were reviewed by Ross *et al.* (1961) following an exhaustive search for anticancer agents. More recently, several bicyclic amino acids have been reported. These include 2-aminoadamantane-2-carboxylic acid, whose peptides can serve as inhibitors of leucine aminopeptidase (Nagasawa *et al.*, 1975). The corresponding norbornane amino acid and its peptides are readily prepared by a Diels–Alder reaction between cyclopentadiene and α-dehydroalanine derivatives, including peptides (Horikawa *et al.*, 1980). The latter process suggests that, given a variety of reactive dienes, a variety of peptide analogs incorporating unusual bicyclic amino acids can be obtained from a single dehydroalanine peptide.

C. Conformationally Constrained Dipeptide Units

A very recent development in the design of peptide hormone analogs is the introduction of bridging groups into an otherwise normal peptide, which provide a secondary linkage between adjacent residues and thereby restrict conformational freedom. This would be expected to enhance receptor affinity if the resulting analog were to approximate the receptor-bound conformation of the native hormone. This type of structural change may also confer resistance to enzymatic degradation on the analogs.

Analysis of the structural relationship between morphine alkaloids and enkephalins led Di Maio *et al.* (1979) to synthesize a series of enkephalin analogs possessing either a methylene bridge between the tyrosine amino

nitrogen and the Gly^2 α-carbon, or an ethano bridge between the same nitrogen and the Gly^2 nitrogen. The resulting Tyr-Gly units can be treated as simple imino acids for the purpose of peptide synthesis. These investigators reported that one of the analogs exhibited potent analgesic activity *in vivo*, the others being inactive (Di Maio *et al.*, 1979; Di Maio and Schiller, 1980).

Some very encouraging results along similar lines have been obtained by the Merck peptide group with LHRH analogs. Following prior evidence of a β-turn at positions 6 and 7 in the active conformation of LHRH, Freidinger, and co-workers (1980) sought to lock the molecule into this conformation by introducing an ethano bridge between the α-carbon of Gly^6 and the nitrogen of Leu^7. The corresponding dipeptide unit was prepared conveniently from Boc-Met-Leu-OMe via a sulfonium salt; this unit was incorporated into positions 6 and 7 of gonadoliberin LHRH using traditional methods. The resulting analog exhibited significantly greater potency *in vitro* and *in vivo* than the native hormone, apparently because of greater receptor affinity. A number of related conformational constraints have been reported (Freidinger, 1981; Freidinger *et al.*, 1982) employing hydrocarbon or thioether bridges in five-, six-, and seven-ring structures, some of which are readily derived from ordinary amino acids. Enkephalin analogs with such bridges between adjacent glycine residues were reported, and some of them exhibited weak but significant activity.

V. REPORTER GROUPS

A. Fluorinated Amino Acids in Nmr Studies of Peptides

A large number of fluorinated derivatives of coded amino acids have been introduced as antimetabolites and antibacterial agents. Among the more interesting fluorinated amino acids available for study are pentafluorophenylalanine and tetrafluorotyrosine (Filler *et al.*, 1969), trifluoromethionine (Dannley and Taborsky, 1957), and aliphatic amino acids bearing CF_3 groups (Lazar and Sheppard, 1968). Although the acidity or basicity of proximal groups is often affected by fluorine substitution, steric differences are minimal. For these reasons, Fauchère and Schwyzer (1971), in describing a synthesis of pentafluorophenylalanine, proposed the use of fluoroamino acids as nmr-active probes that avoid the complexities and interferences in the interpretation of proton nmr data of peptides. Conformational changes occurring upon molecular association, kinetics of association, and nonbonded interactions are all potentially amenable to study using ^{19}F nmr, although very little has been done to date; Schwyzer

and Ludescher (1968) have discussed the relevant methodology in a paper describing the use of proton nmr reporter groups in peptides, and Dwek (1972) has reviewed the use of ^{19}F-nmr probes in the study of macromolecules.

Gerig and McLeod (1976) used a monofluoroproline in proton nmr studies on a tripeptide; the fluorine substituent dispersed the chemical shifts of the proline protons and facilitated the interpretation of individual coupling constants from which the time-averaged ring conformation could be calculated. Blumenstein *et al.* (1981) reported the use of a 3-fluorotyrosine analog of oxytocin in their studies on the binding of neurohypophyseal hormones to neurophysins: The affinity was unchanged by the fluorine substituent; the data indicated that the amino acid residue was conformationally constrained upon binding but experienced a polarity environment similar to that present in the free hormone.

The potential of silicon-containing amino acids for proton nmr studies is also worth mentioning in this context; certain protons in these amino acids will appear considerably upfield from the range in which peptides generally fall and are therefore amenable to convenient study.

B. Spin Labels

Many of the advantages of ^{19}F nmr also apply to esr spectroscopy, with the added advantage of very high sensitivity, resulting in very low working concentrations of the odd-electron species necessary for observation. Stable free radicals are rather limited structurally, and it is not easy to incorporate a radical grouping into a peptide without significant secondary steric and functional perturbation. Weinkam and Jorgensen (1971a,b) have introduced an amino acid approximating histidine in structure, where the imidazole ring is replaced with a dioxyimidazoline structure (nitronyl-nitroxide radical). In simple derivatives, pH-dependent conformational changes were observed and characterized via coupling constants to the β-hydrogens. A series of analogs based on the COOH-terminal three-residue sequence (His-Pro-Phe) of angiotensin II were prepared; standard synthetic techniques were applicable with some restrictions, although the products were generally noncrystalline (possibly because of diastereoisomerism) and required chromatographic purification. pH-dependent ion–dipole interactions of the odd-electron group with the COOH-terminus were observed and interpreted in terms of conformational preferences; the interaction was shown to be dependent on the presence of a proline residue in the sequence. The temperature dependence of the line broadening allowed the determination of activation energies for rotamer interconversion. The functional differences between histidine and the spin-labeled amino acid used in these studies might lead one to question their relevance to the native hormone;

in this case, proton nmr and other studies with the native hormone reinforce these interpretations.

A method of introducing a spin label onto a cysteine residue using a nitroxide-functionalized maleimide was introduced by Möschler and Schwyzer (1974), who also applied the technique to the study of angiotensin II. Here steric differences are considerably greater.

C. Radioactive Labels

The most straightforward labeling technique, namely, the incorporation of a previously radioactively labeled amino acid into a peptide, requires multiple manipulations of radioactively labeled intermediates (a disadvantage and potential hazard), which may cause concomitant loss of label in the case of rapid decay isotopes. Unusual amino acids offer the possibility of incorporating a specific radioactive label at a final stage in the synthesis of a peptide analog, which was formerly achieved only in the case of tyrosine labeling with iodine isotopes. The introduction of tritium via catalytic hydrogenation of unsaturated groups (Felix *et al.*, 1977) or hydrogenolysis of halogenated aromatic amino acids (Eberle and Schwyzer, 1976) may potentially be extended to many of the amino acids of these structural types listed in the Appendix.

In addition to the standard types of radiolabeling, incorporation of unusual isotopes is possible using nonstandard amino acids. Firnau *et al.* (1973) prepared a very hot ^{18}F-labeled β-(3,4-dihydroxyphenyl)alanine (dopa) derivative via a diazonium salt intermediate. The process is potentially applicable to peptides, and the isotope is a γ-emitter suitable for scintigraphic organ imaging. Although exotic, further application of the technique could prove very useful in studying endocrinological processes. A series of ^{123m}Te-labeled amino acids analogous to cysteine and methionine have also been introduced (Knapp *et al.*, 1978).

VI. REACTIVE SIDE-CHAIN FUNCTIONALITY

A. Receptor Interactions

Covalent attachment of a peptide hormone analog to a receptor, enzyme, or other binding site is a highly desirable goal. On the one hand, it makes possible the labeling of such sites with radioactive or fluorescent tags, facilitating isolation and/or structural studies on the binding protein. On the other hand, long-lasting agonist or antagonist activity may result from

such binding; besides being desirable from the standpoint of medicinal chemistry, this allows the study of receptor turnover and other compensatory physiological mechanisms that affect the pharmacology of the system. Two basic strategies exist for bringing about such irreversible binding. The reactive group, such as an alkylating agent, may be present initially, in which case it must be relatively inert to nonspecific side reactions which might take place while the substance is en route to the receptor. Alternatively, the reactive group can be generated at the binding site from a relatively inert precursor. This is most often done photochemically (photoaffinity labeling) but may take place via action of functional groups at the binding site (suicide inactivators), the latter process being generally restricted to enzymes.

1. Alkylating Agents

Amino acids incorporating an alkylating agent in the side chain are known both as natural products (antibiotics), or components thereof, and as synthetic substances originally of interest as potential antitumor compounds. Alkylating functionalities available as components of amino acids include simple alkyl halides, α-halo carbonyl compounds, nitrogen mustards, epoxides, and Michael acceptors. The simple haloaliphatic amino acids are in most cases too unreactive to be practical in this regard, although such effects have apparently never been specifically sought in their derivatives. The other groupings are considerably more reactive and show promise in this application.

Following the introduction of 4-bis(2-chloroethyl)aminophenylalanine (melphalan) as an experimental antitumor agent (Bergel and Stock, 1954; Bergel *et al.*, 1955), a series of related amino acids have appeared that contain the nitrogen mustard grouping. Little has been done in the way of incorporating this amino acid into peptides, and the results are not promising (e.g., 0.3% of the pressor activity of angiotensin II in the 8-melphalan analog), possibly because of steric differences. Still there is a possibility that an irreversible receptor attachment might be demonstrable, not to mention the intriguing possibility that the antitumor (cytotoxic) activity of the amino acid might be channeled much more specifically into hormone-sensitive tumor cells by incorporation of the residue into an appropriate hormone analog. Karpavicius *et al.* (1973) have determined the stability of several such mustards in dioxane–water at 60°C, obtaining rate constants for hydrolysis in the neighborhood of 10^{-3} min^{-1}; this bodes well for the applications referred to above. A handful of epoxy-functionalized amino acids are known, some as components of antibiotics (e.g., chlamydocin, bacilysin) or as antibiotics themselves (anticapsin). Since their antibiotic activity may result from the alkylating ability of the epoxide group, it seems

possible that epoxide-containing peptides could function as irreversibly binding hormone analogs. Olefinic amino acids and their derivatives are potential sources of additional new epoxide structures.

Since Walter *et al.* (1972) reported that placing an α-bromoacetyl group on the NH_2-terminus of oxytocin converted it into an irreversible antagonist of oxytocin-dependent adenylate cyclase, several research groups have been concerned with pursuing similar strategies via modified amino acid side chains. Pliška and Marbach (1978) prepared an oxytocin analog containing a 4-bromoacetamidophenylalanine residue at position 2 (tyrosine) and observed characteristics of irreversible antagonist activity. An isosteric analog of this (CH_3 replacing bromine) gave typical reversible behavior, but the results were not unequivocal. Similar studies were performed with analogs of arginine–vasopressin (Fahrenholz and Thierauch, 1980; Fahrenholz *et al.*, 1980), which were found to have activity similar to that of the native hormone, although irreversibility was not confirmed. The retention of activity in both these cases despite increased steric bulk is encouraging. A bromoketone variant on this amino acid is also known and seems to be a likely candidate for similar experiments.

Among the alkylating agents under discussion, maleimides are unique in being relatively "soft"; in biological systems, they are essentially specific for the free thiol function, with which they undergo Michael addition. Maleimides derived from the ω-amino group of ornithine and lysine have been reported by Keller and Rudinger (1975); the ω-amino group of an ornithine or lysine residue in a peptide can be so functionalized. Applications of these compounds in affinity labeling and in the preparation of conjugates have been suggested.

2. *Photoaffinity Labeling*

Photoaffinity labeling requires a substrate or hormone analog that bears an inert but photochemically activated functional group, giving rise to covalent attachment to a group at the binding site when irradiated in the bound state. This offers several advantages over the "alkylating agent" strategy: The analog remains stable up until the irradiation step, allowing traditional binding studies to be carried out and eliminating ambiguities arising from partial degradation. The reactive species (usually a carbene or a nitrene) can link to almost all types of proximal groups, including unactivated C—H bonds. Limitations of the method include the necessity of working in the dark for most such compounds, possible side reactions in the protein induced by irradiation, and the general inapplicability of the method to in vivo studies. Some very impressive results have been obtained using this method, primarily with enzymes. In peptide chemistry, aryl azides have been exclusively used for this purpose. Although in some instances an

extra azidoaryl group has been attached to a hormone structure to provide a photoaffinity labeling agent, the incorporation of an azido derivative of phenylalanine in place of phenylalanine or tyrosine (or perhaps tryptophan or another amino acid) has the advantage of causing minimal steric differences between the analog and the native hormone.

Schwyzer and Caviezel (1971) introduced 4-azidophenylalanine expressly for such purposes, and succeeding papers from Schwyzer's group illustrate some of its successful applications. For example, chymotrypsin (Escher and Schwyzer, 1974) was successfully labeled using azidophenylalanine-containing tripeptide substrate analogs, which, surprisingly, were in some cases bound more tightly to the enzymes than the corresponding phenylalanine peptide. Variants on this theme, the 3-azido- and 4-azido-3-nitro derivatives, were described and shown to function similarly. A method for introducing a tritium label in the course of synthesizing such photoaffinity peptides was later described and applied in the preparation of a photoactive α-MSH analog (Eberle and Schwyzer, 1976).

Higher degrees of covalent linkage, shorter irradiation times, and longer wavelengths are possible with nitroazidophenylalanine derivatives (perhaps at some sacrifice of binding strength). In one experiment, a 2′-nitro-4′-azido derivative provided 75% labeling in 3 min, as opposed to 40% in 30 min for the corresponding 4′-azido compound (Fahrenholz and Schimmack, 1975). Surprisingly, the nitro group alone was found to give rise to covalent attachment in experiments with chymotrypsin and substrate analogs (Escher and Schwyzer, 1974). This report should be of some interest considering the numerous nitrophenylalanine peptides already described in the literature. Also reported were photoaffinity derivatives of antamanide (Wieland *et al.*, 1971), a leucine aminopeptidase substrate (Escher *et al.*, 1974), a neurophysin-binding tripeptide (Klausner *et al.*, 1978), and arginine–vasopressin (Fahrenholz and Thierauch, 1980).

Several methods are available for introducing the azidophenylalanine residue into a peptide. These include incorporating the preformed azido compound with the use of traditional peptide synthesis (requiring special treatment because of the lability of the azido group toward catalytic hydrogenation and strong acids) or by carrying out transformations on a nitro- or protected aminophenylalanine residue after incorporation into the peptide structure (see Fahrenholz and Thierauch, 1980, for a brief review).

B. Synthetic Transformations on Side-Chain Groups

The development of peptide-based medicinal chemistry has followed a significantly different path from, say, the chemistry of steroids and alkaloids: Derivatization is the exception rather than the rule, and most structural

variants of peptides have been prepared by incorporating a substitute amino acid at an appropriate point in the synthesis. In marked contrast to traditional organic chemistry, each structural variant is prepared via a separate synthesis. Although this may be facilitated by automated techniques or by the sharing of common intermediates in separate syntheses, it remains cumbersome relative to the straightforward reactions by which analogs and congeners are often made in the alkaloid or steroid series. Drug development is facilitated when numerous derivatives are available for testing, increasing the likelihood of a chance discovery, which is still a major route to new drugs. It therefore seems prudent to consider synthetic transformations of side-chain groups as an alternate, and perhaps less costly, strategy for the preparation of analogs of peptides.

A considerable variety of functional-group modification reactions of applicability to the more reactive side chains of the coded amino acids have been developed for use in protein chemistry (Glazer, 1976), and most of these are sufficiently mild by nature as to be directly applicable to typical peptides. Unfortunately, many of these modifications are inappropriate from the standpoint of analog design (many involve the introduction of excessively bulky groups and/or radical changes in functionality); furthermore, multiple reactive sites on a peptide pose problems in some cases. Nevertheless, this approach can provide peptide analogs with desirable biological activity. Rudinger (1972) points out that increasing the steric bulk of selected residues in a peptide hormone often imparts antagonist activity to the analog; clearly such side-chain modifications lend themselves well to this sort of application, and Rudinger cites a large number of successful examples. More recently, as a compelling example of this approach, various modifications of Lys^{12}, His^{1}, and Ser^{2} residues in glucagon were carried out, and some highly potent antagonists were obtained (Hruby *et al.*, 1981; Bregman *et al.*, 1980).

Unusual amino acids can lend themselves to functional group transformations upon preformed peptides. By proper choice of the functional group, the advantages of high selectivity, mild reaction conditions, residue specificity, and a wide choice of modification reactions can be realized, thereby avoiding some of the separation and structure determination problems that beset modifications of native residues. An amino acid with such a specially functionalized side chain may be incorporated into an appropriate position in a peptide structure using traditional methods; the resulting analog serves as a mutual precursor of a series of related analogs obtained by applying a group of specific transformations in parallel. The requirements for such a scheme are that the amino acid be compatible with typical methods of peptide syntheses and that the side-chain transformations are all compatible with the remainder of the peptide structure.

Further advantages of this approach are that sensitive functional groups, which would not survive the conditions used in standard peptide synthesis, may be introduced at a final stage, and that all the analogs in a series have nearly identical chemical histories, lending further credence to comparisons of biological activity (e.g., error sequences and epimerization during construction of the peptide would remain invariant among analogs).

1. Aromatic Side Chains

Two basic types of strategies for modifying an aryl residue on a peptide side chain are presently available, although other possibilities exist besides these. The nitro-amino-diazonium sequence provides a reactive grouping that can be (and has been) nucleophilically substituted in a variety of ways, most notably by azide (Eberle and Schwyzer, 1976) and halide (e.g., Firnau *et al.*, 1973; Houghten and Rapoport, 1974), with other possibilities such as cyano, hydroxy, alkoxy, and "onium" salts suggesting themselves from classical chemistry. Furthermore, the aryl ring at the amino stage may be substituted electrophilically in a variety of ways, only a few of which have been explored. Much of this chemistry is compatible with peptide structures, given proper precautions.

A second strategy involves metallo derivatives of the aryl ring. A series of silylated phenylalanines has been introduced (e.g., Frankel *et al.*, 1963, 1968; Gertner *et al.*, 1963) which, given the known ease of electrophilic substitutions ipso to the silyl group (Eaborn, 1975), may provide for a variety of substitutions with such groups as hydrogen (and its isotopes), heavy metals such as mercury, and iodine and other halogens (possibly in masked form). Similar possibilities exist for boronic acid-functionalized phenylalanine (Roberts *et al.*, 1980) which, after incorporation into a peptide (apparently without interference from the boronic acid group) can be converted under very mild conditions (aqueous, pH $\sim$ 9) to a phenylalanine or tyrosine residue with silver cation or H_2O_2, respectively. An additional asset of the boronic acid group is that it can serve as a "handle" for extractive purification of its derivatives (Kemp and Roberts, 1975). As in the case of silyl derivatives, further known electrophilic substitutions of the boronic group, such as heavy metal reactions, are of potential use in broadening the scope of this strategy.

2. Sulfur-Containing Side Chains

Much of the thiol derivatization chemistry developed for proteins is applicable to cysteine and related residues in peptides. Usually such residues as they occur naturally are components of disulfide bridges; useful application of the divergent modification strategy would probably be limited to

the introduction of a cysteine residue in place of another, followed by the use of various transformations on this residue to provide a series of analogs. Just a few of the many relevant transformations cited by Glazer (1976) include oxidative sulfonation (providing a glutamic acid isolog), reaction with ethyleneimine (giving a "thialysine"), iodoacetic acid (giving a "homothiaglutamic" residue), and peracid oxidation (giving an aspartic acid isolog). Introduction of a spin label grouping is also possible (Möschler and Schwyzer, 1974). Many of the resulting amino acids are known in the uncombined state and have been well-characterized. In some cases, these have been incorporated, using traditional methods, into peptides whose biological activity has been determined. For example, Hermann and Zaoral (1965) found that a thialysine residue (from cysteine and ethyleneimine) in vasopressin greatly decreased pressor activity and enhanced antidiuretic activity of the resulting analog relative to the native lysine–vasopressin. It therefore appears that these variants of amino acids can provide useful analogs.

Further possibilities result from oxidation at the sulfur atom in such "thia" amino acids; this has been done for free thialysine and thiahomoglutamic acid, giving sulfoxides and sulfones (Hermann *et al.*, 1970), but this should be readily applicable to the residue in a peptide as well. Some "selena" analogs of these thia amino acids are known (e.g., DeMarco *et al.*, 1975), and some of the sulfur chemistry is applicable here.

As a further extension of this technology, Wright and Rodbell (1980) have introduced a sulfhydryl group at the 2'-position of tryptophan residues (in this case, in glucagon) and used this grouping in the preparation of conjugates or immobilization of the hormone. Some of the functionalizations of cysteine should apply here also.

3. *Unsaturated Side Chains*

Quite a variety of unsaturated amino acids have been reported in the literature, containing olefin, diene, allene, and acetylene groups of various types. Little has been done to exploit the reactions of these groups, however. A number of them have been proposed or used as a convenient means of introducing deuterium or tritium labels into a peptide (Jansen *et al.*, 1970; Felix *et al.*, 1977). Other processes of potential use that have for the most part been applied only to the amino acid itself and that are known from traditional olefin chemistry (e.g., cyclopropanation, epoxidation, hydroxylation, oxidative cleavage, cycloaddition reactions, metal complex formation) offer a wide range of mild transformations.

In a conscious attempt to employ the "pluripotential" strategy in the preparation of peptide analogs, Synodis and Roberts (1981) made use of

the terminal acetylene grouping in propargylglycine (Schwyzer *et al.*, 1976). Model studies showed that the ethynyl hydrogen could be replaced with silver under mild conditions, and from this deuterio, iodo, and mercuric derivatives could be prepared. Mild hydration to the methyl ketone and partial or total hydrogenation could be carried out as well. No problems were encountered incorporating the residue into an enkephalin analog, and a series of five related enkephalin analogs were prepared by carrying out transformations on the acetylene grouping.

Some especially interesting individual examples of unsaturated amino acids include vinylglycine (Baldwin *et al.*, 1977), a series of allenic amino acids (e.g., Black and Landor, 1968a,b), and a group of structurally related amino acids derived from 2',5'-dihydro-*O*-methyltyrosine (Kaminski and Sokolowska, 1973). In this last case, the dihydroamino acid (obtained by Birch reduction of the aromatic amino acid) can be selectively transformed to provide a choice of saturated or unsaturated ketones or vinyl ethers: These in turn could in principle be used to provide numerous derivatives based on transformations of ketone or olefin groups.

These are a few selected examples of what may develop into a cohesive and well-worked-out chemistry of functional group transformations in peptides. The reader is invited to explore the structures in the Appendix to this chapter, which may suggest themselves for further applications of this strategy.

VII. PEPTIDE ISOSTERES

A relatively recent approach to the design of peptide hormone analogs that departs from the use of coded amino acids is based on modifications of the peptide backbone. This is usually done with the intention of imparting hydrolytic stability or even enzyme inhibitory activity to the analog. Use of β-amino and α-hydrazino acids, often structurally derived from coded amino acids, results in the insertion of an extra atom into the peptide chain, thereby altering the steric relationships between side chains; nevertheless, in some cases, useful biological activity results, and resistance to enzymes is often imparted. This strategy is even employed in nature, as in the carboxyl proteinase inhibitor bestatin. Other minor backbone modifications include reversal of one or more amide linkages (Goodman and Chorev, 1981) and the employment of α-azaamino acids (carbazic acid derivatives).

Replacement of the amide linkage with a sterically similar grouping represents a more formidable synthetic challenge but has the advantage of completely eliminating (rather than displacing) the hydrolytically susceptible

grouping while preserving the steric relationships between side chains. This strategy requires the availability of preformed units bearing the appropriate side chains and incorporating the modified linkage, which have been referred to as dipeptide isosteres or pseudodipeptides. These are formally δ-amino acids and can be incorporated into peptides using traditional methods in most cases. Information concerning sites of *in vivo* enzymatic degradation, which has recently become available for a number of peptide hormones (see, for example, Marks, 1978), greatly assists in suggesting sites for amide bond replacement.

Early efforts along these lines centered on reduced linkages in which the CONH group is replaced with or reduced to a CH_2NH functionality (Zaoral *et al.*, 1967; Atherton *et al.*, 1971; Roeske *et al.*, 1976; Szelke *et al.*, 1977). This introduces a basic or protonated amine at a formerly neutral site and requires protection for further elaboration. More recently, Yankeelov *et al.* (1978) have introduced the CH_2S linkage as an amide bond replacement. Their methods appear applicable to a variety of amino acid starting materials and can preserve chirality at the α-carbon bearing the sulfur. This approach has provided LHRH analogs with high *in vitro* potency (Spatola *et al.*, 1980). More recently, variants on this theme involving CH_2SO, $C(CH_3)S$, and $C(CH_3)SO$ linkages have been introduced (Spatola *et al.*, 1981). A further interesting variant is the thioamide linkage (which may not in fact impart hydrolytic stability), which has been introduced into various peptide structures (Ried and Schmidt, 1966; Jones *et al.*, 1973; Clausen *et al.*, 1981).

Recently, some of the more synthetically challenging amide bond replacements have appeared. Hann *et al.* (1980) prepared an active enkephalin analog employing a trans olefin linkage. Almquist *et al.* (1980) synthesized a potent angiotensin-converting enzyme inhibitor containing a $COCH_2$ linkage at a site corresponding to that which would undergo enzymatic cleavage in the natural substrates. Ondetti's group have overcome some formidable synthetic problems in introducing new methods for preparing dipeptide isosteres involving trans $CH{=}CH$ and $C(=CH_2)CH_2$ linkages, among others (Natarajan *et al.*, 1981).

There is some question as to the degree to which various amide bond replacements affect the conformation space available to a peptide analog. Marshall *et al.* (1981) have introduced procedures by which an analog can be compared to its true peptide congener; they find, for example, the surprising result that the trans olefin linkage is a better mimic of an amide than a retro amide linkage. It is worth mentioning in this context the conformationally constrained dipeptide units introduced by Di Maio *et al.* (1979) and by Freidinger *et al.* (1980) which, like the dipeptide isosteres, may be incorporated into peptides similarly to ordinary amino acids. Farmer (1980) has provided an interesting overview of the "no-man's land" lying between the traditional areas of organic chemistry and peptide chemistry; his viewpoint focuses on the design and synthesis of "nonpeptidic peptidomimetics." It appears that, especially with molecular modeling capabilities such as those used so effectively by the Merck group (Gund *et al.*, 1980), success in the design of such molecules will become sufficiently likely as to justify attempts to solve the formidable synthetic problems they pose.

ACKNOWLEDGMENTS

The authors wish to thank those of our colleagues who kindly made manuscripts and other information available to us for inclusion in this review. Frank Vellaccio is indebted to the Chemistry Department at the University of California, San Diego, for a visiting associate professorship (1981–1982) during which much of this work was completed.

APPENDIX

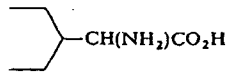
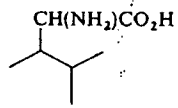
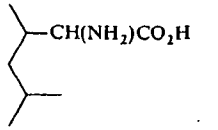
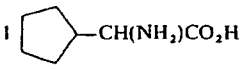
The following tabulation is designed to provide chemists with information about the variety of amino acids available by chemical synthesis. The authors have attempted complete coverage of the literature within certain limitations, as follows: (1) Only α-amino carboxylic acids are included; (2) the parent amino acid is listed in cases where only simple derivatives were reported; (3) all α,α-disubstituted amino acids, with the exception of 1-amino-1-carboxycycloalkanes and related cyclic structures, are excluded; (4) all α-dehydro- and α-azaamino acids are excluded; (5) all simple heteroatom-functionalized (e.g., protected, N-alkylated, etc.) derivatives of genetically coded amino acids are excluded; (6) all noncoded stereoisomers of coded amino acids are excluded; (7) with a few exceptions, all amino acids for which no chemical synthesis exists are excluded; (8) all references to the patent literature are excluded. For some classes of amino acids, explicit listings have been omitted due to the large number of related structures; in these cases, all references are included with a general descriptive term and/or generalized structure.

All physical, chemical, and stereochemical data on the amino acids have been omitted from the table, but these may generally be obtained from the cited references. No attempt has been made to prioritize the references, to include all references to original work, or to give exhaustive bibliographies on each entry. The references were chosen so as to provide the reader with synthetic procedures for each amino acid and examples of its use in peptide synthesis when such use exists. Ultimately, the contents of the table will reflect the subjective opinions of the authors, who are solely responsible for any deficiencies or omissions that may inconvenience the reader, and we apologize for such that may exist.

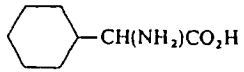
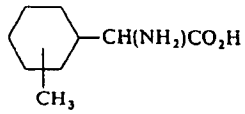
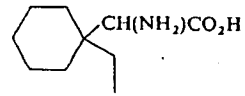
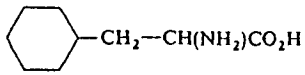
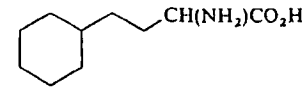
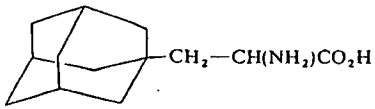
The entries in the table have been arranged according to a system of 20 structural categories, which are listed below; within each category, the authors have attempted to arrange the entries in a systematic and convenient order, although this was not possible in all cases. Amino acids that fall into more than one category are cross-referenced to the additional categories.

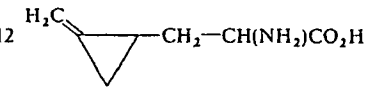
Structural categories of amino acids:

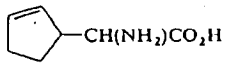
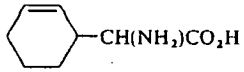
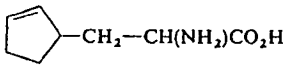
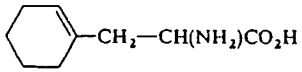
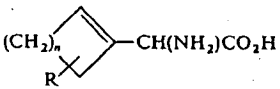
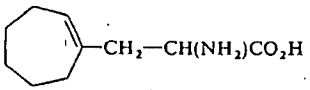
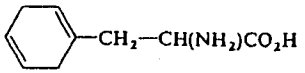
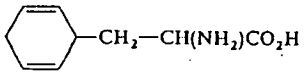
Structure and name	References
Aliphatic: saturated (I)	
I-1 $CH_3(CH_2)_nCH(NH_2)CO_2H$ $n = 1$–8, 11, 15 2-Aminoalkanoic acids	Greenstein and Winitz, 1961
I-2 $(CH_3)_3C—CH(NH_2)CO_2H$ 2-Amino-3,3-dimethylbutanoic acid (*tert*-butylglycine, *tert*-leucine)	Yamada *et al.*, 1977; Pospíšek and Bláha, 1976; Steglich *et al.*, 1971; Pracejus and Winter, 1964
I-3 $(CH_3)_3CCH_2—CH(NH_2)CO_2H$ 2-Amino-4,4-dimethylpentanoic acid	Fauchère and Petermann, 1981
I-4 $CH_3(CH_2)_nCHCH(NH_2)CO_2H$ (CH$_3$ branch) $n = 2$–5 2-Amino-3-methylalkanoic acids	Greenstein and Winitz 1961

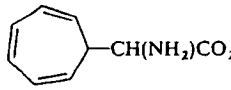
Structure and name	References
I-5 $CH_3CH_2CH(CH_3)CH_2—CH(NH_2)CO_2H$ 2-Amino-4-methylhexanoic acid (homoisoleucine)	Gellert *et al.*, 1978
I-6  β,β-Diethylalanine	Greenstein and Winitz, 1961
I-7  β-Methylleucine	Sheehan and Ledis, 1973; Oki *et al.*, 1970
I-8  2-Amino-3,5-dimethylhexanoic acid	Greenstein and Winitz, 1961
I-9 $R^2—C(R^1)(R^3)—CH(NH_2)CO_2H$ *tert*-Alkylglycines $R^1 = Me$, $R^2 = Me$, $R^3 = Et$*; $R^1 = Et$, $R^2 = Et$, $R^3 = Et$; $R^1, R^2 = (CH_2)_5$, $R^3 = Et$	Schöllkopf and Meyer, 1975; 1977; * See also Jorgensen *et al.*, 1971.
I-10 $(CH_3)_2CH(CH_2)_n—CH(NH_2)CO_2H$ $n = 2, 3, 4$ α-Amino-(ω-1)-methylalkanoic acids (mono-, bis-, and trishomoleucines)	Shiba *et al.*, 1975
I-11  α-Cyclopentylglycine	Hill and Dunn, 1965, 1969; Eisler *et al.*, 1966; Ohno and Izumiya, 1965

(continued)

Structure and name	References
I-12  α-Cyclohexylglycine	Tamura and Harada, 1978; Eisler *et al.*, 1966
I-13  Methylcyclohexylglycines	Greenstein and Winitz, 1961
I-14  α-(1-Ethylcyclohexyl)glycine	Horner and Schwahn, 1955
I-15  3-Cyclohexylalanine	Wieland *et al.*, 1977a; Borin *et al.*, 1977; Kunzi *et al.*, 1974; Fletcher and Young, 1972, 1974; Khosla *et al.*, 1972
I-16  2-Amino-4-cyclohexylbutanoic acid	Greenstein and Winitz, 1961
I-17  3-(1-Adamantyl)alanine	Do and Schwyzer, 1981; Do *et al.*, 1979
See also compounds IX-1–12; X-13; XIV-1–4, 26–33	
Aliphatic: unsaturated (II)	
II-1 $CH_2=CH-CH(NH_2)CO_2H$ 2-Amino-3-butenoic acid (α-vinylglycine)	Afzali-Ardakani and Rapoport, 1980; Baldwin *et al.*, 1977
II-2 $CH_2=C(CH_3)-CH(NH_2)CO_2H$ 2-Amino-3-methyl-3-butenoic acid (α-isopropenylglycine)	Baldwin *et al.*, 1977; Levenberg, 1968

Structure and name	References
II-3 $CH_2=CHCH_2-CH(NH_2)CO_2H$ 2-Amino-4-pentenoic acid (Allylglycine)	Fushiya *et al.*, 1981
II-4 $CH_3CH=CH(CH_2)_nCH(NH_2)CO_2H$ $n = 1, 2$ 2-Amino-4-hexenoic acid (2-Amino-5-heptenoic acid)	Greenstein and Winitz, 1961
II-5 $CH_3CH=C(CH_3)CH_2-CH(NH_2)CO_2H$ 2-Amino-4-methyl-4-hexenoic acid	Edelson *et al.*, 1959
II-6 $(CH_3)_2C=CHCH_2-CH(NH_2)CO_2H$ 2-Amino-5-methyl-4-hexenoic acid	Letham and Young, 1971; Dardenne *et al.*, 1968
II-7 $CH_2=CH(CH_3)CH_2-CH(NH_2)CO_2H$ 2-Amino-4-methyl-5-hexenoic acid	Snider and Duncia, 1981
II-8 $CH_2=CH(CH_2)_3-CH(NH_2)CO_2H$ 2-Amino-6-heptenoic acid	Karwoski *et al.*, 1978
II-9 $CH_2=C(CH_3)-C(CH_3)(CH_3)-CH(NH_2)CO_2H$ 2-Amino-3,3,4-trimethyl-4-pentenoic acid	Altman *et al.*, 1975
II-10 $CH_2=C(Cl)CH_2-CH(NH_2)CO_2H$ 2-Amino-4-chloro-4-pentenoic acid	Hatanaka *et al.*, 1974
II-11 $Cl_2C=CH-CH(NH_2)CO_2H$ 2-Amino-4,4-dichloro-3-butenoic acid	Iwasaki *et al.*, 1976; Urabe *et al.*, 1975
II-12  2-Amino-3-(2-methylenecyclopropyl)-propanoic acid	Black and Landor, 1968c

Structure and name	References
II-13  2-(2-Cyclopentenyl)glycine	Santoso *et al.*, 1981b
II-14  2-(2-Cyclohexenyl)glycine	Santoso *et al.*, 1981a; Dzieduszycka *et al.*, 1978
II-15  3-(2-Cyclopentenyl)alanine, also the 3-enyl derivative	Porter *et al.*, 1968
II-16  3-(1-Cyclohexenyl)alanine (3′,4′,5′,6′-Tetrahydrophenylalanine), also the 2-enyl derivative*	Kaminski and Sokolowska, 1973; *Porter *et al.*, 1968; Snow *et al.*, 1968
II-17  α-(1-Cycloalkenyl)glycines n = 2, 3, 4, 5 and R = H; n = 3 and R = 4-Me	Nunami *et al.*, 1979; Suzuki *et al.*, 1978
II-18  3-(1-Cycloheptenyl)alanine	Porter *et al.*, 1968
II-19  3-(1,4-cyclohexadienyl)alanine (2′,5′-dihydrophenylalanine)	Banerjee *et al.*, 1979; Ressler *et al.*, 1979; Nagarajan *et al.*, 1973; Snow *et al.*, 1968
II-20  3-(2,5-Cyclohexadienyl)alanine (1′,4′-dihydrophenylalanine)	Scholz and Schmidt, 1974

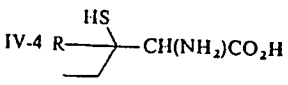
Structure and name	References
II-21  2-(7-Cycloheptatrienyl)glycine	Hanessian and Schütze, 1969
II-22 $H_2C{=}C{=}CHCH_2{-}CH(NH_2)CO_2H$ 2-Amino-4,5-hexadienoic acid (β-allenylalanine); similar amino acids with the ketene functional group can be found in these references	Black and Landor, 1968a,b
II-23 $HC{\equiv}C{-}CH(NH_2)CO_2H$ 2-Amino-3-butynoic acid (ethynylglycine)	Fauchère *et al.*, 1979
II-24 $HC{\equiv}CCH_2CH(NH_2)CO_2H$ Propargylglycine	Schwyzer *et al.*, 1976; Synodis and Roberts, 1981
II-25 $CH_3C{\equiv}CCH_2{-}CH(NH_2)CO_2H$ 2-Amino-4-hexynoic acid	Hatanaka *et al.*, 1972
II-26 $HC{\equiv}CCH{=}CHCH_2{-}CH(NH_2)CO_2H$ 2-Amino-4-hepten-6-ynoic acid	Black and Landor, 1968b
See also structures IV-14, 15; V-20, 36–41; VI-10, 11, 21, 23; VII-13, 14; X-14; XII-81; XIII-5; XIV-9–11, 30; XVIII-4	
Aliphatic: halogenated (III)	
III-1 $FCH_2{-}CH(NH_2)CO_2H$ 3-Fluoroalanine	Kollonitsch *et al.*, 1979; Dolling *et al.*, 1978; Gal *et al.*, 1977; Kollonitsch and Barash, 1976
III-2 $F_3C{-}CH(NH_2)CO_2H$ 3,3,3-Trifluoroalanine	Uskert *et al.*, 1973; Weygand *et al.*, 1966, 1967, 1970b
III-3 $CH_3\underset{\displaystyle F}{\underset{\vert}{C}}H{-}CH(NH_2)CO_2H$ 2-Amino-3-fluorobutanoic acid	Kollonitsch *et al.*, 1979; Loy and Hudlicky, 1976

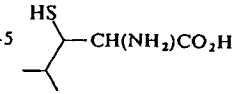
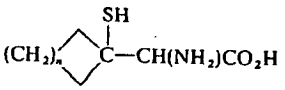
(continued)

Structure and name	References
III-4 $CH_3(CH_2)_nCHCH(NH_2)CO_2H$ (F on CHCH)	Gershon *et al.*, 1973
$n = 1, 2$	
2-Amino-3-fluoroalkanoic acids	
III-5 $RCF_2—CH(NH_2)CO_2H$	Wade and Khéribet, 1980; Wade and Guedj, 1979
2-Amino-3,3-difluorobutanoic acid, 2-amino-3,3-difluoro-3-phenylpropanoic acid (β,β-difluorophenylalanine) R = Me, Ph	
III-6 $CF_3CF_2—CH(NH_2)CO_2H$	Weygand *et al.*, 1970a
2-Amino-3,3,4,4,4-pentafluorobutanoic acid (α-perfluoroethylglycine)	
III-7 $F(CF_2)_n CH_2—CH(NH_2)CO_2H$	Steglich *et al.*, 1967
$n = 2, 3$	
3-Perfluoroalkylalanines	
III-8 $(CH_3)_2C—CH(NH_2)CO_2H$ (F on C)	Gershon *et al.*, 1973
β-Fluorovaline	
III-9 $(CH_2F)_2CH—CH(NH_2)CO_2H$	Lettré and Wölcke, 1967
2-Amino-3-fluoromethyl-4-fluorobutanoic acid (ω,ω'-difluorovaline)	
III-10 $CF_3(CH_2)_2—CH(NH_2)CO_2H$	Babb and Bollinger, 1970
2-Amino-5,5,5-trifluoropentanoic acid	
III-11 $CF_3CH(CH_3)—CH(NH_2)CO_2H$	Babb and Bollinger, 1970; Loncrini and Walborsky, 1964
2-Amino-3-methyl-4,4,4-trifluorobutanoic acid (ω,ω,ω-trifluorovaline)	
III-12 $(CF_3)_2CH—CH(NH_2)CO_2H$	Knunyants and Cheburkov, 1960; Vine *et al.*, 1981
2-Amino-3-trifluoromethyl-4,4,4-trifluorobutanoic acid (ω-hexafluorovaline)	
III-13 $CF_3CF_2CF_2—CH(NH_2)CO_2H$	Weygand *et al.*, 1970a
2-Amino-3,3,4,4,5,5,5-heptafluoropentanoic acid	

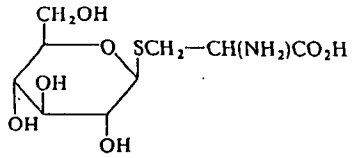
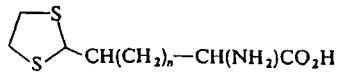
Structure and name	References
III-14 $FCH_2CH_2CH(CH_3)—CH(NH_2)CO_2H$	Hudlicky *et al.*, 1970
2-Amino-3-methyl-5-fluoropentanoic acid (ω-fluoroisoleucine)	
III-15 $CH_3CHFCH(CH_3)—CH(NH_2)CO_2H$	Gershon *et al.*, 1978
2-Amino-3-methyl-4-fluoropentanoic acid (γ-fluoroisoleucine)	
III-16 $CH_3CF_2CH_2CH_2—CH(NH_2)CO_2H$	Hudlicky, 1967
2-Amino-5,5-difluorohexanoic acid	
III-17 $(CH_2F)_2CHCH_2—CH(NH_2)CO_2H$	Lettré and Wölcke, 1967
2-Amino-4-(fluoromethyl)-5-fluoropentanoic acid (ω,ω'-difluoroleucine)	
III-18 $(CF_3)_2CHCH_2—CH(NH_2)CO_2H$	Lazar and Sheppard, 1968
2-Amino-4-trifluoromethyl-5,5,5-trifluoropentanoic acid (ω-hexafluoroleucine)	
III-19 $RRCF—CH(NH_2)CO_2H$	Ayi *et al.*, 1981
3-Fluoro-substituted aliphatic amino acids	
R = R' = Me; R = Me and R' = Et, Ph; R = R' = $(CH_2)_4$, $(CH_2)_5$	
III-20 $ClCH_2—CH(NH_2)CO_2H$	Srinivasan *et al.*, 1977; Okumura *et al.*, 1972
2-Amino-3-chloropropanoic acid (3-chloroalanine)	
III-21 $CH_3CHCl—CH(NH_2)CO_2H$	Srinivasan *et al.*, 1977
2-Amino-3-chlorobutanoic acid	
III-22 $Cl_2CHCH_2—CH(NH_2)CO_2H$	Iwasaki *et al.*, 1976; Urabe *et al.*, 1975
2-Amino-4,4-dichlorobutanoic acid	
III-23 $Cl_3CCH_2—CH(NH_2)CO_2H$	Iwasaki *et al.* 1976; Urabe *et al.*, 1974
2-Amino-4,4,4-trichlorobutanoic acid	

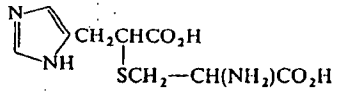
(continued)

Structure and name	References
III-24 $Cl_3CCH(Cl)—CH(NH_2)CO_2H$ 2-Amino-3,4,4,4-tetrachlorobutanoic acid	Urabe *et al.*, 1974
III-25 $ClCH_2—(CH_2)_3—CH(NH_2)CO_2H$ 2-Amino-6-chlorohexanoic acid	Effenberger and Karlheinz, 1979
III-26 $Br—CH_2CH_2—CH(NH_2)CO_2H$ 2-Amino-4-bromobutanoic acid	Nollet *et al.*, 1969
III-27 $CH_3CH(Br)—CH(NH_2)CO_2H$ 2-Amino-3-bromobutanoic acid	Wieland *et al.*, 1977b
See also structures II-10, 11; V-18, 19, 35; VI-12–15; VII-15, 16; VIII-8; IX-19; XI-1, 4; XII-5–9, 13, 14, 21, 22, 26, 35–39, 41, 42, 48, 49, 53–58; XIII-14, 16; XIV-5–8; XV-4, 5, 12; XVI-5, 7; XVII-2–7, 22, 34; XIX-7, 8	
Aliphatic: chalcogen-containing (IV)	
IV-1 $HSCH(CH_3)—CH(NH_2)CO_2H$ 2-Amino-3-mercaptobutanoic acid (β-methylcysteine)	Morell *et al.*, 1977
IV-2 $HS\text{-}CH_2CH_2CH(NH_2)CO_2H$ Homocysteine	Greenstein and Winitz, 1961
IV-3 $HS—C(CH_3)_2—CH(NH_2)CO_2H$ Penicillamine (3-mercaptovaline)	Sheehan and Yang, 1958 (see also Greenstein and Winitz, 1961)
IV-4  3-Mercaptonorvaline (3-mercaptoisoleucine) R = H, CH_3	Greenstein and Winitz, 1961

Structure and name	References
IV-5  3-Mercaptoleucine	Greenstein and Winitz, 1961
IV-6 $HSCH(CH_3)—CH(CH_3)—CH(NH_2)CO_2H$ 2-Amino-3-methyl-4-mercaptopentanoic acid	Zdansky, 1968a
IV-7 $HSC(CH_3)_2CH_2—CH(NH_2)CO_2H$ 2-Amino-5-mercapto-5-methylhexanoic acid	Dilbeck *et al.*, 1978
IV-8  n = 1, 2, 3 (1-Mercaptocycloalkyl)glycines	Leclercq *et al.*, 1978
IV-9 $CH_3S(CH_2)_3CH(NH_2)CO_2H$ Homomethionine	Greenstein and Winitz, 1961
IV-10 $CH_3S(CH_2)_4—CH(NH_2)CO_2H$ 2-Amino-6-(methylthio) hexanoic acid (bishomomethionine)	Lee and Serif, 1970
IV-11 $CH_3SCH_2CH(C_6H_5)CH(NH_2)CO_2H$ β-Phenylmethionine	Greenstein and Winitz, 1961
IV-12 $Et—S\text{-}CR^1R^2CH_2CH—CH(NH_2)CO_2H$ Also *S*-*n*-butyl derivatives R′ = Me, R = R^2 = H; R′ = Me, R = R^2 = Me; R′ = Ph, R = R^2 = H; R′ = H, R = R^2 = H	Rakhshinda and Khan, 1978

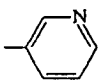
(continued)

Structure and name	References
IV-13 $R—CH(NH_2)CO_2H$ "Thia" amino acids R = amino acid side chain in which a sulfur atom replaces a CH_2 group	Hermann, 1981
IV-14 $CH_3CH=CHS(O)CH_2—CH(NH_2)CO_2H$ 3-(1-Propenesulfinyl)alanine, also the 2-enyl derivative (alliine)	Nishimura *et al.*, 1975; Stoll and Seebeck, 1951
IV-15 $CH_3SCH=CH—CH(NH_2)CO_2H$ 2-Amino-4-(methylthio)-3-butenoic acid (Δ^3-dehydromethionine)	Balenovic and Deljac, 1973
IV-16 $PhCH_2S—CH(NH_2)CO_2H$ α-(Benzylthio)glycine	Matthies, 1978; Petrzilka and Fehr, 1973
IV-17 $CH_3S(CH_2)_2CH(OH)—CH(NH_2)CO_2H$ 2-Amino-3-hydroxy-5-(methylthio)-pentanoic acid	Otani and Briley, 1974
IV-18 $HOCH_2CH_2C(CH_3)_2SCH_2—CH(NH_2)CO_2H$ *S*-(2-Methyl-4-hydroxy-2-butyl)cysteine	Schöberl *et al.*, 1968; Trippett, 1957
IV-19  *S*-(β-Glucopyranosyl)cysteine	Monsigny *et al.*, 1977
IV-20  $n = 0, 1, 2$ α-Amino-1,3-dithiolane-2-alkanoic acids	Mertes and Ramsey, 1969

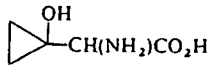
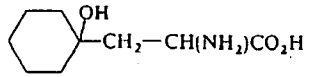
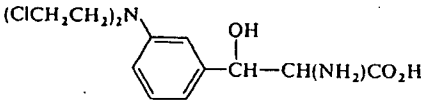
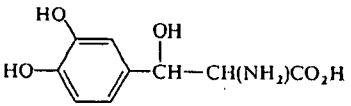
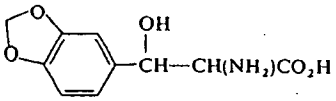
Structure and name	References
IV-21 $H_2NC(=S)CH_2—CH(NH_2)CO_2H$ 2-Aminobutanedioic acid 4-thionamide (γ-thioasparagine)	Ressler and Banerjee, 1976
IV-22  *S*-[1-Carboxy-2-(4-imidazolyl)ethyl]cysteine	Yankeelov and Jolley, 1972
IV-23 $PhSO_2—CH(NH_2)CO_2H$ α-Benzenesulfonylglycine	Matthies, 1978
IV-24 $RCH_2SO_2CH_2CH(NH_2)CO_2H$ γ-Thialysine and -homoglutamic acid *S,S*-dioxides $R = H_2NCH_2, HO_2C$	Hermann *et al.*, 1970
IV-25 $HO_3SCH_2—CH(NH_2)CO_2H$ Cysteic acid	Bodanszky *et al.*, 1977
IV-26 $XO_2S—CH_2—CH(NH_2)CO_2H$ Cysteic acid derivatives $X = NH_2$ $X = NHR$ or $NH—NHR$ $X = Cl$ $X = SH$	Aleksiev *et al.*, 1971 Brynes *et al.*, 1978 Stoev *et al.*, 1973 DeMarco and Coletta, 1961
IV-27 $CH(NH_2)CO_2H$ CH_2SO_2H Cysteine sulfinic acid (β-sulfinylalanine)	Gordon, 1973
IV-28 $HS—SO_2—CH_2CH_2—CH(NH_2)CO_2H$ 2-Amino-4-thiosulfobutanoic acid	DeMarco and Luchi, 1972
IV-29 $HSeCH_2—CH(NH_2)CO_2H$ Selenocysteine	Shrift *et al.*, 1976; for a review, see Walter, 1973; Zdansky, 1973

(continued)

Structure and name	References
IV-30 $HSeCH(CH_3)CH(CH_3)—CH(NH_2)CO_2H$ 2-Amino-3-methyl-4-hydroselenopentanoic acid	Zdansky, 1968a
IV-31 $RSeCH_2CH_2—CH(NH_2)CO_2H$ Selenomethionine and Se-alkyl congeners R = Me, Et, Bzl	Zdansky, 1968b; Jakubke *et al.*, 1968
IV-32 $CH_3SeCH_2CH(CH_3)—CH(NH_2)CO_2H$ 2-Amino-3-methyl-4-(methylseleno)butanoic acid	Zdansky, 1967
IV-33 $RCH_2SeCH_2CH(NH_2)CO_2H$ γ-Selenalysine, R = H_2NCH_2 γ-Selenahomoglutamic acid, R = HO_2C	DeMarco *et al.*, 1975 Rinaldi *et al.*, 1976
IV-34 $H_2N(CH_2)_3SeCH_2—CH(NH_2)CO_2H$ 3-(3-Aminopropylseleno)alanine (γ-selenahomolysine)	DeMarco *et al.*, 1976
IV-35 $CH_3TeCH_2CH_2—CH(NH_2)CO_2H$ Telluromethionine	Knapp, 1979
See also structures VII-24, 25; IX-13; XI-4; XII-82; XIV-12, 13, 44–50; XVI-10; XVII-11, 19; 14; XVIII-14	
Aliphatic: oxygenated (V)	
V-1 $HOCH_2CH_2—CH(NH_2)CO_2H$ 2-Amino-4-hydroxybutanoic acid	Turan and Manning, 1977
V-2 $CH_3CH_2CH(OH)CH_2CH(NH_2)CO_2H$ γ-Hydroxynorleucine (also δ and ε)	Greenstein and Winitz, 1961
V-3 $CH_3(CH_2)_nCHOHCH(NH_2)CO_2H$ n = 1, 2, 14 2-Amino-3-hydroxyalkanoic acids	Ariyoshi and Sato, 1971; Ichikawa *et al.*, 1971; Greenstein and Winitz, 1961

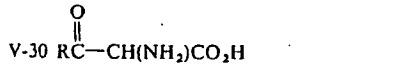
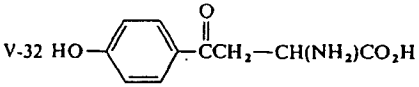
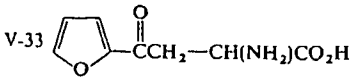
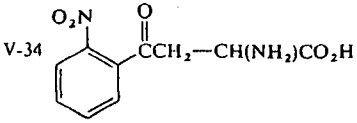
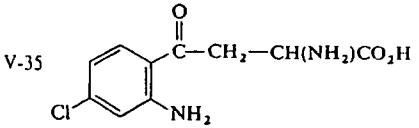
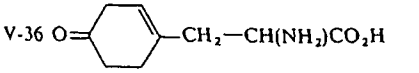
Structure and name	References
V-4 $HOCH_2CH(CH_3)—CH(NH_2)CO_2H$ 2-Amino-3-methyl-4-hydroxybutanoic acid (homothreonine)	Usher, 1980
V-5 $(CH_3)_2C(OH)—CH(NH_2)CO_2H$ 3-Hydroxyvaline (3-methylthreonine)	Scott and Wilkinson, 1981; Berse and Bessette, 1971; Obhashi and Harada, 1966
V-6 $HO(CH_2)_4—CH(NH_2)CO_2H$ 2-Amino-6-hydroxyhexanoic acid	Dreyfuss, 1974; Davis and Bailey, 1972
V-7 $CH_3CH_2CH(OH)CH_2—CH(NH_2)CO_2H$ 2-Amino-4-hydroxyhexanoic acid (also 4-oxo derivative)	Barry and Roark, 1964
V-8 $(CH_3)_2CHCH(OH)—CH(NH_2)CO_2H$ 3-Hydroxyleucine	Futagawa *et al.*, 1971
V-9 $CH_3CH_2C(OH)(CH_3)—CH(NH_2)CO_2H$ 3-Hydroxyisoleucine (3-ethylthreonine)	Dobson and Vining, 1968
V-10 $HOCH_2C(CH_3)_2—CH(NH_2)CO_2H$ 3-(Hydroxymethyl)valine	Ackermann and Shive, 1948
V-11 $R—CH(OH)—CH(NH_2)CO_2H$ Various β-hydroxyamino acids R = H, Me, Et, $CH(CH_3)_2$, CO_2H, Ph, *p*-Ph-NO_2, 	Ozaki *et al.*, 1979b

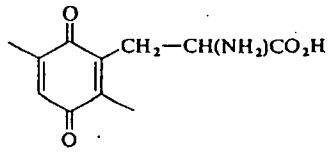
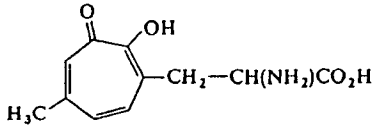
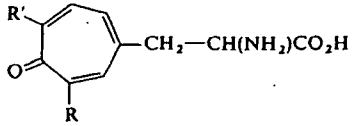
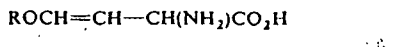
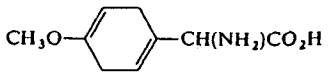
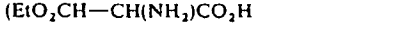
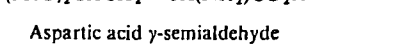
(continued)

Structure and name	References
V-12  α-(1-Hydroxycyclopropyl)glycine (3,4-methylenethreonine)	Kato *et al.*, 1980
V-13  3-(1-Hydroxycyclohexyl) alanine	Snow *et al.*, 1968
V-14 $PhCH(OH)-CH(NH_2)CO_2H$ β-Hydroxyphenylalanine (β-phenylserine) carbohydrate derivative	Arold and Reissmann, 1970 Weiss, 1977
V-15  3-Hydroxy-3′-(bis(2-chloroethyl)amino)-phenylalanine, also para derivative	Straukas *et al.*, 1971
V-16  3,3′,4′-Trihydroxphenylalanine (β-hydroxydopa)	Hegedüs *et al.*, 1975
V-17  3-Hydroxy-3′,4′-methylenedioxyphenylalanine, many other derivatives	Eisele, 1975
V-18 $FCH_2CH(OH)-CH(NH_2)CO_2H$ 4-Fluorothreonine	Lettré and Wölcke, 1967
V-19 $Cl_3CCH(OH)-CH(NH_2)CO_2H$ 4,4,4-Trichlorothreonine	Iwasaki *et al.*, 1976

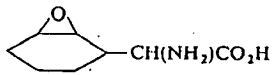
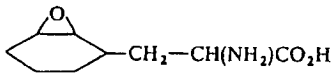
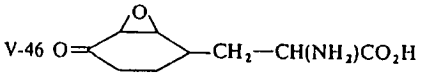
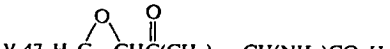
Structure and name	References
V-20 $CH_3C{\equiv}CCH(OH)-CH(NH_2)CO_2H$ 2-Amino-3-hydroxy-4-hexynoic acid	Nimura and Hatanaka, 1974
V-21 $HOCH_2(CHOH)_nCH(NH_2)CO_2H$ $n = 1, 3$ 2-Amino-3,4-dihydroxybutanoic acid (2-amino-3,4,5,6-tetrahydroxyhexanoic acid	Greenstein and Winitz, 1961
V-22 $HOCH_2CH(OH)CH(CH_3)-CH(NH_2)CO_2H$ 2-Amino-4,5-dihydroxy-3-methylpentanoic acid	Georgi and Wieland, 1966
V-23 $HOCH_2CH(OH)(CH_2)_2-CH(NH_2)CO_2H$ 2-Amino-5,6-dihydroxyhexanoic acid	Davis and Bailey, 1972 Mechanic and Tanzer, 1970
V-24 $(HOCH_2)_2CHCH_2-CH(NH_2)CO_2H$ ω,ω′-Dihydroxyleucine	Bory *et al.*, 1979
V-25 $(HOCH_2)_2C(OH)CH_2-CH(NH_2)CO_2H$ 2-Amino-4,5-dihydroxy-4-hydroxymethyl-pentanoic acid	Weygand and Mayer, 1968
V-26 $PhCH_2OCH_2CH_2CH(OH)-CH(NH_2)CO_2H$ 2-Amino-3-hydroxy-5-benzyloxypentanoic acid	Wakamiya *et al.*, 1981
V-27 $H_2N(CH_2)_2-O-CH_2-CH(NH_2)CO_2H$ O-(2-Aminoethyl)serine (4-oxalysine)	Tesser and Nefkens, 1959
V-28 $H_2N(CH_2)_2-O-(CH_2)_2-CH(NH_2)CO_2H$ 2-Amino-4-(2-aminoethoxy)butanoic acid (5-oxahomolysine)	Liu *et al.*, 1978
V-29 $HC(=O)CH_2-CH(NH_2)CO_2H$ Aspartic γ-semialdehyde (β-formylalanine)	Fushiya *et al.*, 1981; Westerik and Wolfenden, 1974

(continued)

Structure and name	References
V-30  Various β-keto α-amino acids (reduction gives corresponding β-hydroxy compound) R = Me, iPr, Ph, Bzl	Kirihata *et al.*, 1978; Ben-Ishai *et al.*, 1975b
V-31  4-Oxoisoleucine	Perlman *et al.*, 1977
V-32  β-(*p*-Hydroxybenzoyl)alanine [2-amino-4-oxo-4-(4-hydroxyphenyl) butanoic acid	Keller-Schierlein and Joos, 1980
V-33  2-Amino-4-oxo-4-(2-furyl)butanoic acid	Ichihara *et al.*, 1973; Couchman *et al.*, 1973
V-34  2-Amino-4-oxo-4-(2-nitrophenyl)butanoic acid	Rivett and Stewart, 1976
V-35  2-Amino-4-oxo-4-(2-amino-4-chlorophenyl)-butanoic acid	Kawashima *et al.*, 1980
V-36  3-(4-Oxo-1-cyclohexenyl)alanine, also saturated compound	Kaminski and Sokolowska, 1973

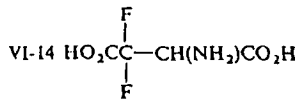
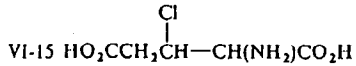
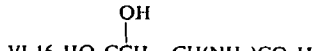
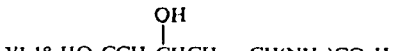
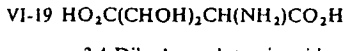
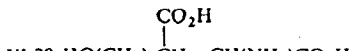
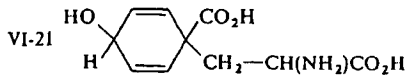
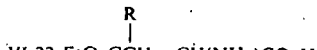
Structure and name	References
V-37  3-(2,5-Dimethyl-3,6-dioxo-1, 4-cyclohexadienyl)alanine	Martynov *et al.*, 1967
V-38  3-(1-Hydroxy-5-methyl-7-oxo-cyclohepta-1,3,5-trien-2-yl)alanine	Teitei, 1979
V-39  3-(1-Hydroxy-7-oxo-cyclohepta-1,3,5-trien-3-yl)alanine (also 4-yl isomer) R = H, R′ = OH; R = OH, R′ = H	Teitei and Harris 1979
V-40  Various 2-amino-4-alkoxy-3-butenoic acids R = Me R = $CH_2CH_2NH_2$ R = $CH_2CH(NH_2)CH_2OH$	Keith *et al.*, 1978a Keith *et al.*, 1978b Keith *et al.*, 1975
V-41  2′,5′-Dihydro-O-methyltyrosine, also 4,5-saturated analog	Kaminski and Sokolowska, 1973
V-42  2-Aminomalonic acid semialdehyde diethyl acetal (3,3-diethoxyalanine)	Teshima *et al.*, 1976
V-43  Aspartic acid γ-semialdehyde dimethyl acetal	Altman *et al.*, 1975

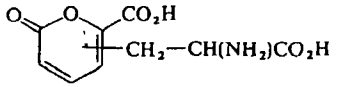
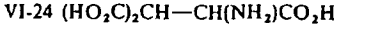
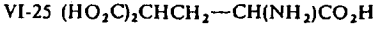
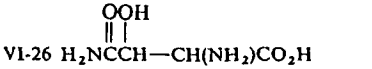
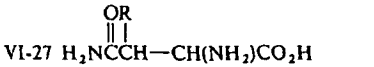
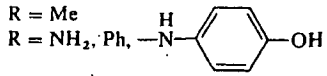
(continued)

Structure and name	References
V-44  α-(2,3-Epoxycyclohexyl)glycine	Dzieduszycka *et al.*, 1978
V-45  3-(2,3-Epoxycyclohexyl)alanine	Borowski *et al.*, 1979
V-46  3-(2,3-Epoxy-4-oxocyclohexyl)alanine	Laguzza and Ganem, 1981; Richards *et al.*, 1977
V-47  2-Amino-8-oxo-9,10-epoxydecanoic acid	Closse and Huguenin, 1974
See also structures IV-17–20; VI-16–21, 26; VII-17–19, 26, 27; VIII-9–10; IX-17; X-5–8; XII-60; XIII-6; XIV-14–20, 35, 36, 42, 43, 50; XV-11; XIX-1, 2; XX-1	
Aliphatic: aminopolycarboxylic acids and derivatives (IV)	
VI-1 $HO_2C-CH(NH_2)CO_2H$ Aminomalonic acid	Fujino *et al.*, 1976
VI-2 $HO_2CCH(CH_3)-CH(NH_2)CO_2H$ β-Methylaspartic acid	Traynham and Williams, 1962; Barber *et al.*, 1959
VI-3 $HO_2CC(CH_3)_2-CH(NH_2)CO_2H$ β,β-Dimethylaspartic acid	Greenstein and Winitz, 1961
VI-4 $HO_2CCH(CH_3)CH_2-CH(NH_2)CO_2H$ γ-Methylglutamic acid	Done and Fowden, 1952

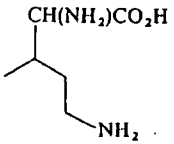
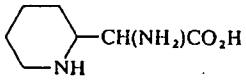
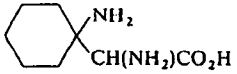
Structure and name	References
VI-5 $HO_2CCH_2CH(R)CH(NH_2)CO_2H$ Various 3-substituted glutamic acid derivatives; R = CH_3, C_6H_5, OH, CO_2H	Greenstein and Winitz, 1961
VI-6 $HO_2CCH(R)CH_2-CH(NH_2)CO_2H$ Various γ-alkylglutamic acids R = Et, *n*Pr, isoamyl, Ph	Shakhnazaryan *et al.*, 1968
VI-7 $HO_2C(CH_2)_nCH(NH_2)CO_2H$ n = 3, 4, 7 2-Aminoalkanedioic acids	Greenstein and Winitz, 1961
VI-8 $HO_2C(CH_2)_5-CH(NH_2)CO_2H$ 2-Aminooctanedioic acid	Veber *et al.*, 1976; Hase *et al.*, 1968
VI-9 $HO_2C(CH_2)_9-CH(NH_2)CO_2H$ 2-Aminododecanedioic acid	Fabrichnyi *et al.*, 1979
VI-10 $HO_2CC(=CH_2)-CH(NH_2)CO_2H$ β-Methyleneaspartic acid	Dowd and Kaufman, 1979
VI-11 $HO_2CCCH_2-CH(NH_2)CO_2H$ γ-Methyleneglutamic acid	Marcus *et al.*, 1963
VI-12 $HO_2CCH(F)-CH(NH_2)CO_2H$ β-Fluoroaspartic acid	Matsumoto *et al.*, 1979
VI-13 $HO_2CCHCH_2(F)-CH(NH_2)CO_2H$ γ-Fluoroglutamic acid	Tolman and Veres, 1966

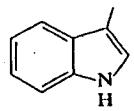
(continued)

Structure and name	References
VI-14 	Hageman *et al.*, 1977
β,β-Difluoroaspartic acid	
VI-15 	Alekseeva *et al.*, 1968
β-Chloroglutamic acid	
VI-16 	Jones *et al.*, 1969; Inui *et al.*, 1968; Liwschitz *et al.*, 1962, 1968a,b; Hedgcoth and Skinner, 1963
β-Hydroxyaspartic acid	
VI-17 	Kusumi *et al.*, 1978; Lee and Kaneko, 1973b; Kaneko *et al.*, 1962
γ-Hydroxyglutamic acid	
VI-18 	Kristensen *et al.*, 1980
2-Amino-4-hydroxyhexanedioic acid (other similar amino acids in this reference)	
VI-19 	Greenstein and Winitz, 1961
3,4-Dihydroxyglutamic acid	
VI-20 	Kuss, 1967a
3-(3-Hydroxypropyl)aspartic acid	
VI-21 	Danishefsky *et al.*, 1981
3-(1-Carboxy-4-hydroxy-2-cyclodienyl)-alanine	
VI-22 	Ozaki *et al.*, 1979a
3-Substituted aspartic acids	
R = Ac, CN	

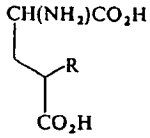
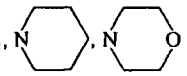
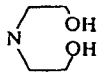
Structure and name	References
VI-23 	Senoh *et al.*, 1964, 1967; Imamoto *et al.*, 1966
3-(2-Carboxy-6-oxo-6*H*-pyranyl)alanines	
VI-24 	Henson *et al.*, 1981
β-Carboxyaspartic acid	
VI-25 	Zee-Cheng and Olson, 1980; Danishefsky *et al.*, 1979; Hiskey and Boggs, 1977; Märki *et al.*, 1977; Oppliger and Schwyzer, 1977
γ-Carboxyglutamic acid	
VI-26 	Singerman and Liwschitz, 1968
β-Hydroxyasparagine	
VI-27 	Brain, 1963 Chang *et al.*, 1973
Various *β*-substituted asparagines	
R = Me R = NH_2, Ph, 	
See also structures IV-21, 22, 24, 33; VII-20–22, VIII-12; IX-14, 19; XI-7, 12; XII-30, 44, 62; XIV-23; XV-13; XVI-20, 21	
Aliphatic: polyamino mono- and polycarboxylic acids and derivatives (VII)	
VII-1 H_2NCH_2—$CH(NH_2)CO_2H$	Waki *et al.*, 1981; Wakamiya *et al.*, 1977; Asquith and Carthew, 1972; Kitagawa *et al.*, 1969; McCord *et al.*, 1968; Asquith *et al.*, 1977
β-Aminoalanine	
VII-2 $CH_3CH(NH_2)CH(NH_2)CO_2H$	Atherton and Meienhofer, 1972
2,3-Diaminobutanoic acid	

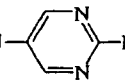
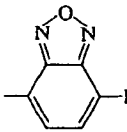
(continued)

Structure and name	References
VII-3 $H_2NCH_2CH_2—CH(NH_2)CO_2H$ 2,4-Diaminobutanoic acid	Ferderigos and Katsoyannis, 1977; El-Maghraby, 1976; Hase *et al.*, 1972; Poduška and Rudinger, 1966
VII-4 $H_2NCH_2—CH(CH_3)—CH(NH_2)CO_2H$ 2,4-Diamino-3-methylbutanoic acid Also (along with 3-phenyl)	Shaw *et al.*, 1981 Greenstein and Winitz, 1961
VII-5 $CH_3CH(NHCH_3)—CH(NH_2)CO_2H$ 2-Amino-3-methylaminobutanoic acid	McCord *et al.*, 1967
VII-6  β-Methylornithine	Skinner and Johansson, 1972
VII-7 $H_2N(CH_2)_3CH(NH_2)CO_2H$ Homolysine	Bodanszky and Lindeberg, 1971
VII-8 $H_2N—CH(C_3H_7)CH_2CH(NH_2)CO_2H$ 2,4-Diaminoheptanoic acid	Greenstein and Winitz, 1961
VII-9  α-(2-Piperidyl)glycine	Golding and Smith, 1980
VII-10  α-(1-Aminocyclohexyl)glycine	Rakhshinda and Khan, 1979
VII-11 $Ph—CH(NH_2)—CH(NH_2)CO_2H$ β-Aminophenylalanine	Ali and Khan, 1978

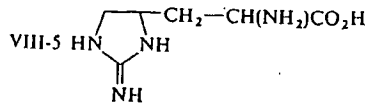
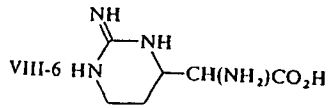
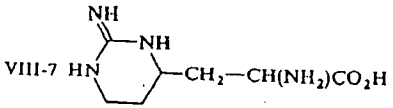
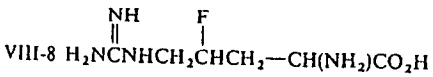
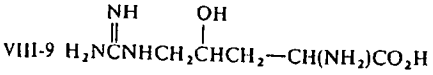
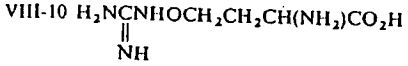
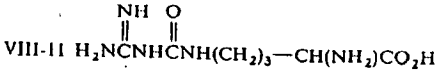
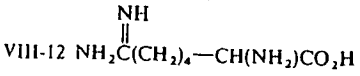
Structure and name	References
VII-12 $R—CH(NH_2)CH(NH_2)CO_2H$ Various α,β-diamino acids R = 4-HOC_6H_4; 4-$MeOC_6H_4$; 4-$Me_2NC_6H_4$; 3,4-$(MeO)_2C_6H_3$; 3,4-methylenedioxy-C_6H_3; 3-MeO-4-HOC_6H_3; $PhCH_2CH_2$; *n*-C_3H_7, 	Rakhshinda and Khan, 1979
VII-13 $H_2NCH_2CH=CHCH_2—CH(NH_2)CO_2H$ 2,6-Diamino-4-hexenoic acid (4,5-dehydrolysine)	Davis *et al.*, 1973
VII-14 $NH_2CH_2C\equiv CCH_2—CH(NH_2)CO_2H$ 2,6-Diamino-4-hexynoic acid	Sasaki and Bricas, 1980; Jansen *et al.*, 1969, 1970
VII-15 $H_2NCH_2CH(F)(CH_2)_n—CH(NH_2)CO_2H$ $n = 1, 2$ 4-Fluoroornithine (5-fluorolysine)	Tolman and Benes, 1976
VII-16 $H_2NCH_2CX_2CH_2CH_2—CH(NH_2)CO_2H$ 5,5-Dimethyllysine (5,5-difluorolysine) X = F or Me	Shirota *et al.*, 1977b
VII-17 $H_2N(CH_2)_nCH(OH)—CH(NH_2)CO_2H$ $n = 2$ $n = 3$ β-Hydroxyornithine and -lysine	Wakamiya *et al.*, 1977; Tomlinson and Viswanatha, 1973 Stammer and Webb, 1969
VII-18 $H_2N(CH_2)_nCHCH_2CH(NH_2)CO_2H$ (OH) $n = 1$ $n = 2$ γ-Hydroxyornithine and -lysine	Greenstein and Winitz, 1961 Fujita *et al.*, 1965

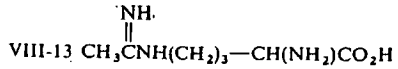
(continued)

Structure and name	References
VII-19 $H_2NCH_2CH_2\overset{\overset{O}{\|}}{C}CH_2—CH(NH_2)CO_2H$ 4-Oxolysine	Hider and John, 1972
VII-20 $(—CH_2CH_2CH(NH_2)CO_2H)_2$ 2,7-Diaminooctanedioic acid	Jošt and Rudinger, 1967; Rudinger and Jošt, 1964
VII-21 $H_2N(CH_2)_3\overset{\overset{CO_2H}{\|}}{C}H—CH(NH_2)CO_2H$ 3-Carboxylysine	Kuss, 1967b
VII-22  3-Substituted glutamic acid derivatives	
R = CH_2NH_2, $CH_2CH_2N(C_2H_5)_2$	Alekseeva *et al.*, 1971c
R = $N(C_2H_5)_2$, 	Alekseeva *et al.*, 1971a
R = 	Alekseeva *et al.*, 1971b
VII-23 $H_2NCH_2CH_2\overset{\overset{NH_2}{\|}}{C}H—CH(NH_2)CO_2H$ β-Aminoornithine	Wakamiya *et al.*, 1978
VII-24 $H_2N(CH_2)_2—X—CH_2—CH(NH_2)CO_2H$ γ-Aza-, thia-, and selenalysines X = NH X = S X = Se	Kolc, 1969; Hermann *et al.*, 1970; Hermann and Zaoral, 1965 Sadeh *et al.*, 1976
VII-25 $\overset{\overset{CH_2CH_2CH(NH_2)CO_2H}{\|}}{S}CH_2CH(NH_2)CO_2H$ Cystathionine	Jošt and Rudinger, 1967; Rudinger and Jošt, 1964; see also Greenstein and Winitz, 1961
VII-26 $H_2NOCH_2CH_2CH(NH_2)CO_2H$ 2-Amino-4-aminooxybutanoic acid (canaline)	Greenstein and Winitz, 1961

Structure and name	References
VII-27 $HONH—(CH_2)_3CH(NH_2)CO_2H$ N^δ-hydroxyornithine	Isowa *et al.*, 1972
VII-28 O_2N-  -$NH(CH_2)_3—CH(NH_2)CO_2H$ N^δ(5-Nitro-2-pyrimidinyl)ornithine	Signor *et al.*, 1971
VII-29 O_2N-  -$NH—(CH_2)_2—CH(NH_2)CO_2H$ 2-Amino-4-(7-nitro-2,1,3-benzoxadiazol-4-ylamino)-butanoic acid	Moore, 1978
See also structures IV-24, 33, 34; V-27, 28, 35, 40; VI-23; IX-15, 16; X-7; XI-8; XII-19, 21, 22, 44, 49; XIV-21, 22, 34; XVI-7, 19; XVII-12, 13; XIX-20	
Aliphatic: guanido- and amidino-containing (VIII)	
VIII-1 $H_2N\overset{\overset{NH}{\|}}{C}NHCH_2—CH(NH_2)CO_2H$ β-Guanidoalanine	Zaoral *et al.*, 1979; Brtnik and Zaoral, 1976
VIII-2 $H_2N\overset{\overset{NH}{\|}}{C}NH\overset{\overset{CH_3}{\|}}{C}H—CH(NH_2)CO_2H$ 2-Amino-3-guanidobutanoic acid	Brtnik and Zaoral 1976
VIII-3 $H_2N\overset{\overset{NH}{\|}}{C}NH(CH_2)_2—CH(NH_2)CO_2H$ 2-Amino-4-guanidobutanoic acid	Van Nispen *et al.*, 1977a; Van Nispen and Tesser, 1972
VIII-4 $H_2N\overset{\overset{X}{\|}}{C}NH(CH_2)_4CH(NH_2)CO_2H$ Homoarginine, homocitrulline X = NH, O	Greenstein and Winitz, 1961

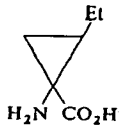
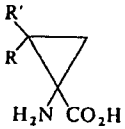
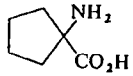
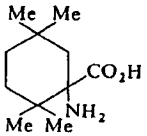
(continued)

Structure and name	References
VIII-5  3(2-Iminoimidazolin-4-yl)-alanine (γ-cycloarginine, enduracididine)	Tsuji *et al.*, 1975
VIII-6  α-(2-Iminohexahydropyrimidin-4-yl)glycine (β-cycloarginine)	Wakamiya *et al.*, 1978; Shiba *et al.*, 1977; Bycroft *et al.*, 1968, 1971
VIII-7  3-(2-Iminohexahydropyrimidin-4-yl)alanine	Iinuma *et al.*, 1977; Tsuji *et al.*, 1975
VIII-8  γ-Fluoroarginine	Tolman and Benes, 1976
VIII-9  γ-Hydroxyarginine	Mizusaki and Makisumi, 1981; Bell, 1961
VIII-10  2-Amino-4-guanidooxybutanoic acid (canavanine)	Greenstein and Winitz, 1961; for derivative, see Rosenthal, 1975
VIII-11  N^{ω}-Amidinocitrulline	Ito and Hashimoto, 1969
VIII-12  2-Aminoheptanedioic acid 7-monoamidine	Culvenor *et al.*, 1969, 1971

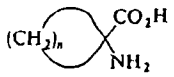
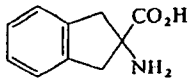
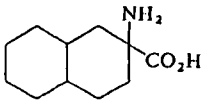
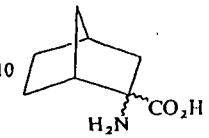
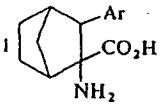
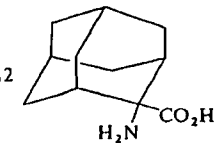
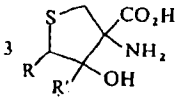
Structure and name	References
VIII-13  N^{δ}-Acetimidoylornithine	Pinker *et al.*, 1975

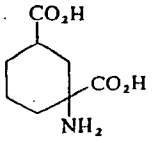
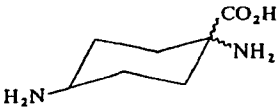
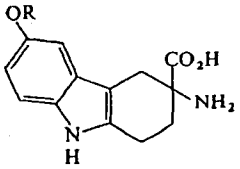
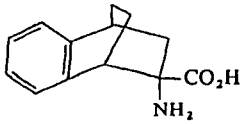
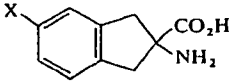
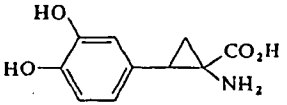
See also structures X-9, 10; XII-23; XIV-54

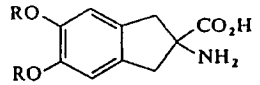
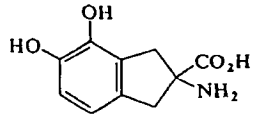
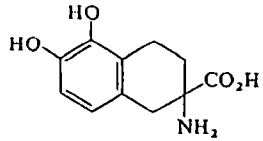
Aliphatic: 1-aminocycloalkane-1-carboxylic acids and related compounds (IX)

IX-1	 1-Aminocyclopropanecarboxylic acid	Rich and Tam, 1978; Bregovec and Jakovčić, 1972
IX-2	 1-Amino-2-ethylcyclopropanecarboxylic acid	Ichihara *et al.*, 1977; Shiraishi *et al.*, 1977
IX-3	 Various 2,2-disubstituted 1-amino-cyclopropanecarboxylic acids	Schöllkopf *et al.*, 1973
IX-4	 1-Aminocyclopentanecarboxylic acid (cycloleucine)	Park *et al.*, 1974; Diehl and Bowen, 1965
IX-5	 1-Aminocyclohexanecarboxylic acid	Kenner *et al.*, 1965
IX-6	 1-Amino-2,2,5,5-tetramethyl-cyclohexanecarboxylic acid	Cremlyn *et al.*, 1970

(continued)

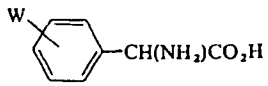
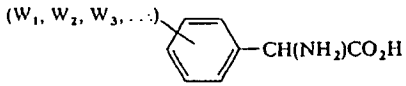
Structure and name	References
IX-7  $n = 7, 9$ 1-Aminocycloheptane- and -nonanecarboxylic acids	Cremlyn *et al.*, 1970
IX-8  2-Aminoindan-2-carboxylic acid	Hsieh *et al.*, 1979
IX-9  2-Aminodecalin-2-carboxylic acid	Chisholm *et al.*, 1967
IX-10  2-Aminonorbornane-2-carboxylic acid	Horikawa *et al.*, 1980
IX-11  3-Aryl-2-aminonorbornane-2-carboxylic acids	Kinoshita *et al.*, 1969
IX-12  2-Aminoadamantane-2-carboxylic acid	Nagasawa *et al.*, 1975
IX-13  Substituted 3'-aminotetrahydrothiophene-3-carboxylic acids $R = R' = (CH_2)_4$; R = H, R' = Ph	Field, 1979

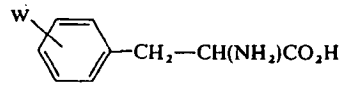
Structure and name	References
IX-14  1-Amino-1,3-cyclohexanedicarboxylic acid	Gass and Meister, 1970
IX-15  3-Aminopyrrolidine-3-carboxylic acid	Monteiro, 1973
IX-16  1,4-Diaminocyclohexanecarboxylic acid	Bey *et al.*, 1978
IX-17  6-Alkoxy-3-amino-1,2,3,4-tetrahydrocarbazole-3-carboxylic acids	Maki *et al.*, 1973
IX-18  2-Aminobenzobicyclo[2.2.2]octane-2-carboxylic acid	Grunewald *et al.*, 1980
IX-19  5-Substituted 2-aminoindan-2-carboxylic acids X = OH, OMe, CO_2H, Cl, Br, I	Pinder *et al.*, 1971
IX-20  1-Amino-2-(3,4-dihydroxyphenyl)cyclopropanecarboxylic acid (2,3-methylene-dopa)	Hines *et al.*, 1976

Structure and name	References
IX-21 	Taylor *et al.*, 1970
5,6-Dialkoxy-2-aminoindan-2-carboxylic acids	
IX-22 	Cannon *et al.*, 1974
4,5-Dihydroxy-2-aminoindan-2-carboxylic acid	
IX-23 	Cannon *et al.*, 1974
5,6-Dihydroxy-2-aminotetralin-2-carboxylic acid	
See also structure XIV-33. Additional examples in this structural class have been cited by Ross *et al.*, 1961.	
Aliphatic: miscellaneous (X)	
X-1 $NCCH(NH_2)CO_2H$	Warren *et al.*, 1974
Aminomalonic acid mononitrile (α-cyanoglycine)	
X-2 $NCCH_2CH(NH_2)CO_2H$	Wilchek *et al.*, 1968; Liberek *et al.*, 1966
Aspartic acid 4-nitrile	
X-3 $NCCH_2CH_2—CH(NH_2)CO_2H$	Wilchek *et al.*, 1968
Glutamic acid 5-nitrile	
X-4 $O_2N—(CH_2)_n—CH(NH_2)CO_2H$ $n = 3$ $n = 4$	Maurer and Keller-Schierlein, 1969; Keller-Schierlein and Maurer, 1969; Bayer and Schmidt, 1973
2-Amino-ω-nitroalkanoic acids	
X-5 $N_2CH_2\overset{O}{\overset{\|}{C}}OCH_2—CH(NH_2)CO_2H$	Curphey and Daniel, 1978; Moore *et al.*, 1954
O-Diazoacetylserine (azaserine)	

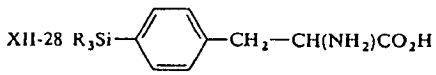
Structure and name	References
X-6 $N_2CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2—CH(NH_2)CO_2H$	Dion *et al.*, 1956
2-Amino-5-oxo-6-diazohexanoic acid	
X-7 $H_2NOCH_2CH_2—CH(NH_2)CO_2H$	Korpela *et al.*, 1977; Gilon *et al.*, 1967
2-Amino-4-aminooxybutanoic acid (δ-oxaornithine)	
X-8 $ONN\overset{OH}{\overset{\|}{C}}H_2—CH(NH_2)CO_2H$	Eaton *et al.*, 1973; Isowa *et al.*, 1973
2-Amino-3-(*N*-nitrosohydroxylamino)propanoic acid	
X-9 $H_2N\overset{O}{\overset{\|}{C}}NHCH_2—CH(NH_2)CO_2H$	Kjaer and Larsen, 1959
β-Ureidoalanine	
X-10 $H_2N\overset{O}{\overset{\|}{C}}NH(CH_2)_2—CH(NH_2)CO_2H$	Izumiya and Kitagawa, 1958
Norcitrulline	
X-11 $(HO)_2\overset{X}{\overset{\|}{P}}CH_2—CH(NH_2)CO_2H$	Varlet *et al.*, 1979
β-Phosphoalanine, thiophosphoalanine	
X = O, S	
X-12 $H_3C\overset{OH}{\overset{\|}{\underset{\|}{P}}}CH_2CH_2—CH(NH_2)CO_2H$ (O)	Gruszecka *et al.*, 1979; Ogawa *et al.*, 1973
2-Amino-4-methanephosphonylbutanoic acid	
X-13 $R—CH_2—\overset{CH_3}{\overset{\|}{\underset{\|}{Si}}}CH_2—CH(NH_2)CO_2H$ (CH_3)	Birkofer and Ritter, 1958; Porter and Shive, 1968
β-Trimethylsilylalanine (R = H); also β-Dimethyl(trimethylsilylmethyl)silylalanine (R = $(CH_3)_3Si$)	
X-14 $Me_3Si—C\equiv C—CH(NH_2)CO_2H$	Casara and Metcalf, 1978
2-Amino-4-trimethylsilyl-3-butynoic acid	
See also structure XII-28, 50; XIII-21–24	

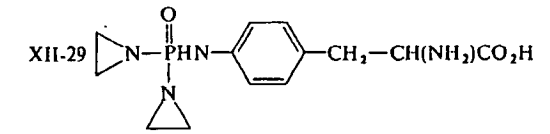
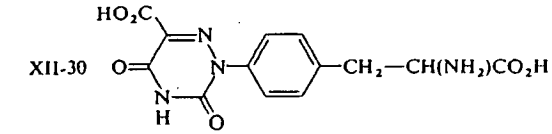
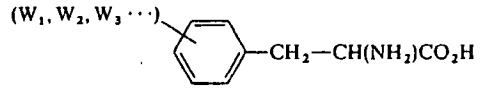
(continued)

Structure and name	References
Carbocyclic aromatic: phenylglycine derivatives (XI)	
	
XI-1 W = H, *m*-Cl, *p*-Cl, *o*-F, *m*-F, *p*-F, *m*-Me, *p*-Me, *p*-OMe	Compere and Weinstein, 1977
XI-2 W = H, *o*-Me	Greenstein and Winitz, 1961
XI-3 W = *p*-OMe	Weinges *et al.*, 1980
XI-4 W = *p*-CH_2Cl, *p*-CH_2OH, *p*-CH_2SMe, *p*-CH_2Br, *p*-CH_2OMe, *p*-CH_2NHBzl	Ben-Ishai *et al.*, 1977a,b
See also	Ben-Ishai *et al.*, 1975a
XI-5 W = *p*-OH	Yamada *et al.*, 1978, 1979
XI-6 W = *m*-OH	Müller and Schütte, 1968
XI-7 W = *m*-CO_2H	Larsen and Wieczorkowska, 1977; Irreverre *et al.*, 1961
XI-8 W = *p*-NH_2, *p*-N_3	Eberle *et al.*, 1981; Fahrenholz and Thierauch, 1980
	
XI-9 W = 3-*t*Bu-4-OH	Lundt *et al.*, 1979
XI-10 W = 3,5-di-F-4-OH	Kirk, 1980
XI-11 W = 3,5-di-OH	Müller and Schütte, 1968
XI-12 W = 3-CO_2H-4-OH	Larsen and Wieczorkowska, 1977
XI-13 W = 3,5-di-*t*Bu-4-OH	Teuber *et al.*, 1978; Hewgill and Webb, 1977

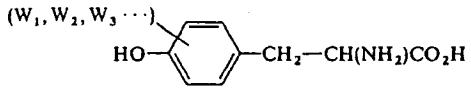
Structure and name	References
Carbocyclic aromatic: phenylalanine derivatives (XII)	
Ring-substituted phenylalanines	
	
XII-1 W = *o*-Me	Berger *et al.*, 1973
XII-2 W = *p*-Et	Zhuze *et al.*, 1964
XII-3 W = *p*-C_6H_5	Yabe *et al.*, 1976
XII-4 W = *p*-CH_2Ph	Podkoscielny *et al.*, 1978
XII-5 W = *m*-F, *p*-Me	Bosshard and Berger 1973; Maki *et al.*, 1977
XII-6 W = *p*-F	Borin *et al.*, 1977; Maki *et al.*, 1977 Bosshard and Berger, 1973; Nicolaides *et al.*, 1963
XII-7 W = *p*-Cl	Houghten and Rapoport, 1974
XII-8 W = *o*-Cl	Greenstein and Winitz, 1961
XII-9 W = *p*-Br, *o*-Br	Faulstich *et al.*, 1973
XII-10 W = *m*-OH	Bernardi *et al.*, 1966
XII-11 W = *o*-OH	Greenstein and Winitz, 1961
XII-12 W = *p*-SH	Greenstein and Winitz, 1961
XII-13 W = *m*-CF_3	Nicolaides and Lipnik, 1966; Maki *et al.*, 1977; Nestor *et al.*, 1982a
XII-14 W = *p*-CF_3	Nestor *et al.*, 1982a for additional fluorinated phenylalanines, see Maki *et al.*, 1977

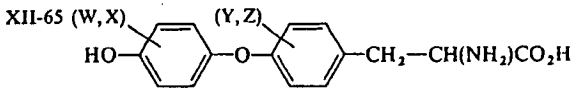
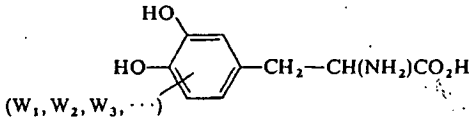
(continued)

Structure and name	References
XII-15 W = *p*-CH_2OH	Smith and Sloane, 1967
XII-16 W = *m*-CH_2OH, *m*-CH_2NH_2	Larsen and Wieczorkowska, 1977
XII-17 W = *m*-CO_2H	Thompson *et al.*, 1961
XII-18 W = *p*-NO_2	Fauchère and Schiller, 1981; Massey and Fessler, 1976; Houghten and Rapoport, 1974; Coy *et al.*, 1974
XII-19 W = *p*-$NH_2(N_3)$	Klausner *et al.*, 1978; Sakarellos *et al.*, 1976; Houghten and Rapoport, 1974; Coy *et al.*, 1974; Schwyzer and Caviezel, 1971
XII-20 W = *p*-CN, *p*-$COCH_3$	Cleland, 1969
XII-21 W = *p*-$N(CH_2CH_2Cl)_2$	Hsieh and Marshall, 1981; Park *et al.*, 1974; Bergel *et al.*, 1955; Bergel and Stock, 1954
XII-22 W = *p*-$N(CH_2CH(Cl)CH_3)_2$	Karpavicius *et al.*, 1973
XII-23 W = *p*-guanidino	Moore *et al.*, 1977b
XII-24 W = *p*-N=N—Ph	Goodman and Kossoy, 1966
XII-25 W = *p*-$CH{=}CHC_6H_5$	Jones and Wright, 1971
XII-26 W = *p*-$COCH_2Br$, *p*-$NHCOCH_2Br$, *m*-$NHCOCH_2Cl$	Degraw *et al.*, 1968
XII-27 W = *p*-$(HO)_2B$	Snyder *et al.*, 1958; Roberts *et al.*, 1980
XII-28  Ortho derivative	Frankel *et al.*, 1963, 1967, 1968; Gertner *et al.*, 1963; for other related derivatives, see Rotman *et al.*, 1967

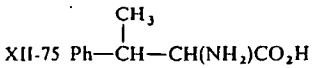
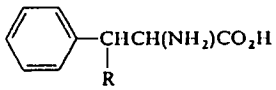
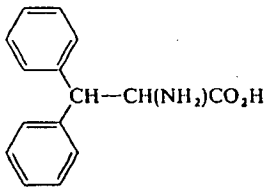
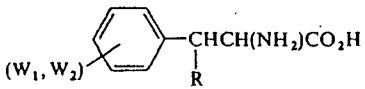
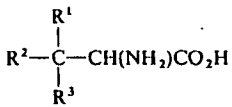
Structure and name	References
XII-29 	Poskiene *et al.*, 1976
XII-30 	Slouka, 1978
Ring-polysubstituted phenylalanines	
	
XII-31 W = 2,4-di-Me; 2,3-di-Me; 2,5-di-Me; 2,6-di-Me; 3,5-di-Me	Greenstein and Winitz, 1961
XII-32 W = 2,4,6-tri-Me	Greenstein and Winitz, 1961
XII-33 W = 3,4,5-tri-Me	Nestor *et al.*, 1982a
XII-34 W = 2,3,4,5,6-penta-Me	Van Nispen *et al.*, 1977b; Coy *et al.*, 1974; Carrion *et al.*, 1968
XII-35 W = 2,4-di-F; 3,4-di-F; 3,5-di-F; 2,5-di-F; 2,6-di-F; 2,3,5,6-tetra-F; 3,5-di-Cl-2,4,6-tri-F	Prudchenko, 1970
XII-36 W = 2,3-di-F; 2,4-di-F; 2,3-bis-CF_3; 2,4-bis-CF_3; 2-Cl-5-CF_3; 4-Cl-5-CF_3; 2,5-di-F	Märki *et al.*, 1977
XII-37 W = 2,3,4,5,6-penta-F	Kaurov and Smirnova, 1977; Bosshard and Berger, 1973; Fauchère and Schwyzer, 1971; Filler *et al.*, 1969
XII-38 W = 2,3-Br; 2,5-Br; 3,4-Br	Faulstich *et al.*, 1973
XII-39 W = 3,4,5-tri-I	Schatz *et al.*, 1968
XII-40 W = 2,3-di-OH; 2,5-di-OH; 2,6-di-OH	Greenstein and Winitz, 1961

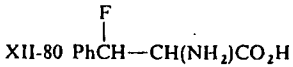
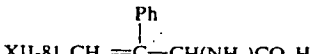
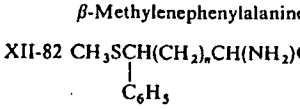
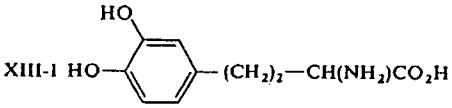
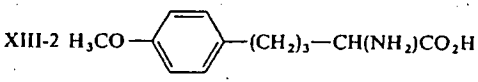
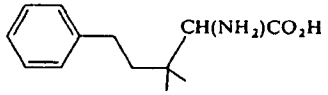
(continued

Structure and name	References
XII-41 W = 3-Br-5-OMe	Crooij and Eliaers, 1969
XII-42 W = 2,5-di-OMe; 2,5-di-OMe-4-Me; 4-Br-2,5-di-OMe	Coutts and Malicky, 1974
XII-43 W = 2,5-di-OMe-4-Me	Lee *et al.*, 1971
XII-44 W = 3-CO_2H-4-OH; 3-CO_2H-4-NH_2	Larsen and Wieczorkowska, 1977
XII-45 W = 2-OH-5-NO_2; 2-OEt-5-NO_2	Greenstein and Winitz, 1961
XII-46 W = 3,4,5-tri-OMe	Nestor *et al.*, 1982a
XII-47 W = 2-NO_2-4-N_3	Fahrenholz and Schimmack, 1975
XII-48 W = 3-$NHCOCH_2Cl$-4-F	Degraw *et al.*, 1968
XII-49 W = 4-$N(CH_2CH_2Cl)_2$-2-OMe	Teng and Pang, 1978
XII-50 W = 2,4-bis-$SiMe_3$	Frankel *et al.*, 1968
Ring-substituted tyrosines	
	
XII-51 W = 3,5-di-*t*Bu	Teuber and Krause, 1978; Teuber *et al.*, 1978
XII-52 W = 3,5-di-Me (O-Me derivative)	Jean and Anatol, 1969
XII-53 W = 3-$CH_2C_6H_5$; 3-$CH_2C_6H_3Cl_2$	Erickson and Merrifield, 1973
XII-54 W = 3-F	Blumenstein *et al.*, 1981
XII-55 W = tetra-F	Filler and Kang, 1965
XII-56 W = 3,5-di-Cl	Brody and Spencer, 1968
XII-57 W = 3-I	Harington and Rivers, 1944
XII-58 W = 3,5-di-I	Lemaire *et al.*, 1977
XII-59 W = 2-OH	Greenstein and Winitz, 1961

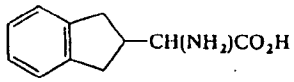
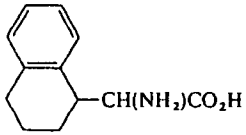
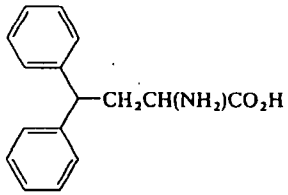
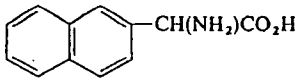
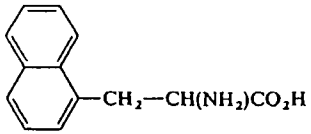
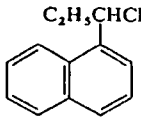
Structure and name	References
XII-60 W = 3-CH_2OH	Wang and Vida, 1974
XII-61 W = 2-OH-6-Me	Schneider, 1958
XII-62 W = 3-CO_2H	Arnold and Larsen, 1977; Leonard *et al.*, 1965; Larsen and Kjaer, 1962
XII-63 W = 3,5-di-NO_2	Brundish and Wade, 1973
XII-64 W = 3-^{211}At-5-I	Visser *et al.*, 1979
XII-65  Variously substituted thyronines	Jorgensen *et al.*, 1969, 1974; Cox *et al.*, 1974; Block and Coy, 1972; Jorgensen and Berteau, 1971; Jorgensen and Wright, 1970a,b; Matsuura *et al.*, 1968, 1969
Ring-substituted dihydroxyphenylalanine (dopa) derivatives	
	
XII-66 W = 2-Cl; 2-Br; 2-F; 2-NO_2	Greenstein and Winitz, 1961
XII-67 W = 2-Me; 2-Et; 2-iPr; 2-*t*Bu-4,5-di-OH	Morgenstern *et al.*, 1971
XII-68 W = 3-F-4,5-di-OH	Firnau *et al.*, 1973
XII-69 W = 2-F-4,5-di-OH	Firnau *et al.*, 1980
XII-70 W = 2,5,6-tri-F-3,4-di-OH	Filler and Rickert, 1981
XII-71 W = 2,6-di-Br-3,4-di-OH; 5,6-di-Br-3,4-di-OH	Anhovry *et al.*, 1974
XII-72 W = 2,4,5-tri-OH	Ong *et al.*, 1969; Langemann and Scheer, 1969
XII-73 W = 2,3,4-tri-OH	Rapp *et al.*, 1975

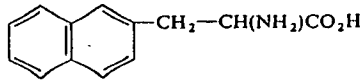
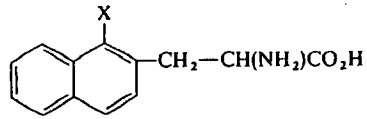
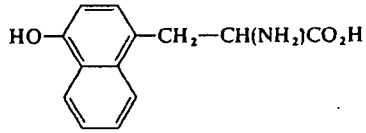
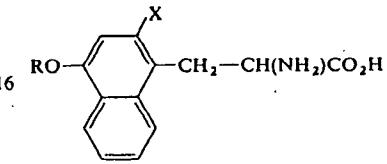
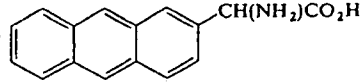
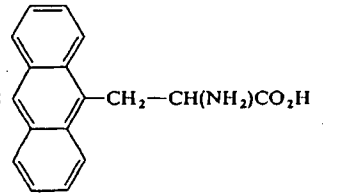
(continued)

Structure and name	References
XII-74 W = 5-OMe-3,4-di-OH	Sethi *et al.*, 1973
Miscellaneous phenylalanine congeners	
XII-75 	Cativiela and Melendez, 1981; Yamada *et al.*, 1977; Kataoka *et al.*, 1976; Arold *et al.*, 1969, 1974; Waisuisz *et al.*, 1957
β-Methylphenylalanine	
XII-76 	Horner and Schwahn, 1955
Various β-substituted phenylalanine derivatives	
R = C_2H_5, i-C_3H_7, *n*-C_4H_9, $PhCH_2$, $PhCH_2CH_2$, *p*-ClC_6H_4, *p*-$MeOC_6H_4$	
XII-77 	Filler and Rao, 1961
β,β-Diphenylalanine	
XII-78 	Horner and Schwahn, 1955
Ring-substituted β-alkylphenylalanines	
R = *n*-C_4H_9, W = *p*-NEt_2; R = C_2H_5, W = *p*-NEt_2; R = C_2H_5, W = 3,4-$(MeO)_2$; R = C_2H_5, W = 3,4-$(OH)_2$	
XII-79 	Schöllkopf and Meyer, 1975, 1977
Various *tert*-aralkyl glycines	
R^1 = Me, R^2 = Me, R^3 = Ph; R^1 = Et, R^2 = Et, R^3 = Ph; R^1 = Me, R^2 = Ph, R^3 = Et; R^1 = Me, R^2 = Ph, R^3 = Ph; R^1 = $(CH_2)_5$, R^2 = $(CH_2)_5$, R^3 = Ph	

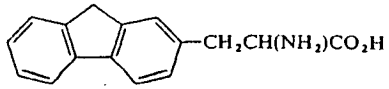
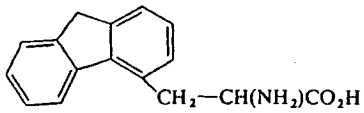
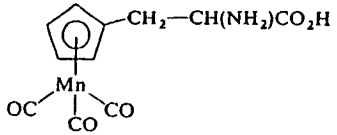
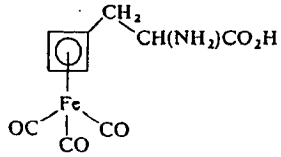
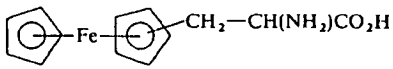
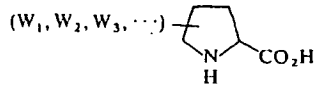
Structure and name	References
XII-80 	Tsushima *et al.*, 1980; Kollonitsch *et al.*, 1979; Wade *et al.*, 1979
β-Fluorophenylalanine	
XII-81 	Chari and Wemple, 1979
β-Methylenephenylalanine	
XII-82 	Greenstein and Winitz, 1961
n = 0, 1	
3-(Methylmercapto)phenylalanine, also γ-phenylmethionine	
See also structures II-19, 20; III-5; IV-11; V-11, 14–17, 30, 36, 37, 41; VI-5, 21, 27; VII-4, 11, 12; XIV-37, 39–41	
Carbocyclic aromatic: miscellaneous (XIII)	
XIII-1 	Winn *et al.*, 1975
2-Amino-4-(3,4-dihydroxyphenyl)butanoic acid (homo-dopa) also the 3,4,5-trihydroxy derivative	
XIII-2 	Shimohigashi *et al.*, 1976, 1977
2-Amino-5-(4-methoxyphenyl)pentanoic acid	
XIII-3 $C_6H_5(CH_2)_nCH(NH_2)CO_2H$	Greenstein and Winitz, 1961
n = 2, 3	
2-Amino-ω-phenylalkanoic acids	
XIII-4 	Horner and Schwahn, 1955
2-Amino-3,3-dimethyl-5-phenylpentanoic acid	
XIII-5 $PhCH{=}CH{-}CH(NH_2)CO_2H$	Hines *et al.*, 1976
2-Amino-4-phenyl-3-butenoic acid (styrylglycine)	

(continued)

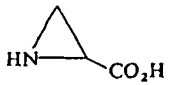
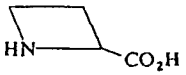
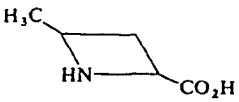
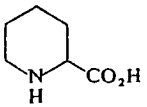
Structure and name	References
XIII-6 $C_6H_5O(CH_2)_nCH(NH_2)CO_2H$ $n = 2, 3$ 2-Amino-ω-phenoxyalkanoic acids	Greenstein and Winitz, 1961
XIII-7  α-(2-Indanyl)glycine	Porter and Shive, 1968
XIII-8  α-(1-Tetralyl)glycine	Reimann and Voss, 1977; Milkowski *et al.*, 1970
XIII-9  Benzhydrylalanine	Nestor *et al.*, 1982a
XIII-10  α-(β-Naphthyl)glycine	Compere and Weinstein, 1977; Ben-Ishai *et al.*, 1975a
XIII-11  3-(1-Naphthyl)alanine	Yabe *et al.*, 1976, 1977, 1978; Nestor *et al.*, 1982a
XIII-12  2-Amino-3-(1-naphthyl)pentanoic acid	Horner and Schwahn, 1955

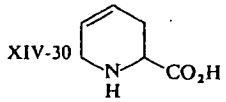
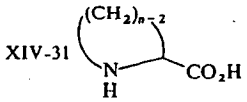
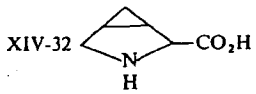
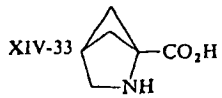
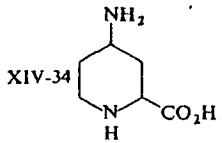
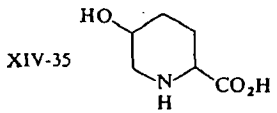
Structure and name	References
XIII-13  3-(2-Naphthyl)alanine	Yabe *et al.*, 1976, 1977, 1978; Berger *et al.*, 1973
XIII-14  3-(1-Chloro-2-naphthyl)alanine, also the bromo derivative:	McCord *et al.*, 1976 see also Nestor *et al.*, 1982a
XIII-15  3-(4-Hydroxy-1-naphthyl)alanine.	Tsou *et al.*, 1966
XIII-16  Various substituted 3-(1-naphthyl)alanines R = H, X = H; R = Me, X = H; R = H, X = Cl; R = Me, X = Cl	Ablewhite and Wooldridge, 1967
XIII-17  α-(2-Anthryl)glycine	Ben-Ishai *et al.*, 1975a
XIII-18  β-(9-Anthryl)alanine	Schreiber and Lautsch, 1965; Nestor *et al.*, 1982a

(continued)

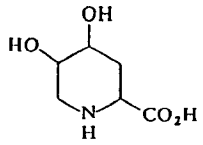
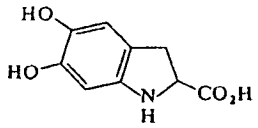
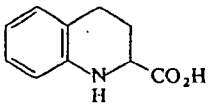
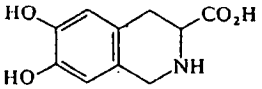
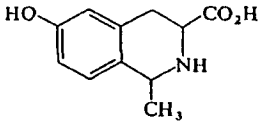
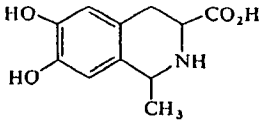
Structure and name	References
XIII-19  3-(2-Fluorenyl)alanine	Nestor *et al.*, 1982a
XIII-20  3-(4-Fluorenyl)alanine	Morrison, 1965
XIII-21  2-Amino-2-carboxyethylcyclopentadienyl manganese tricarbonyl	Brunet *et al.*, 1981a
XIII-22  2-Amino-2-carboxyethylcyclobutadiene iron tricarbonyl	Brunet *et al.*, 1981a
XIII-23  *β*-Ferrocenylalanine	Pospišek *et al.*, 1980; Cuingnet *et al.*, 1980; Hanzlik *et al.*, 1979; Osgerby and Pauson, 1958.
XIII-24 $(B_{10}C_2H_{11})CH_2CH(NH_2)CO_2H$ *β-o*-Carboranylalanine	Schwyzer *et al.*, 1981; Fauchère *et al.*, 1979; Leukart *et al.*, 1976
See also structures IV-12, 16, 23; V-32, 34, 35; VI-6; VII-12; IX-11, 13, 18–23; XIV-37–41, 49; XVI-18; XIX-11, 12	
Heterocyclic: imino acids, including proline analogs (XIV)	
Substituted prolines 	

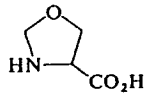
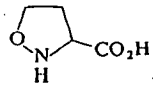
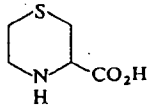
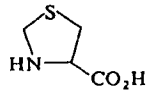
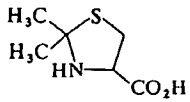
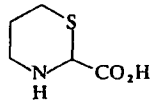
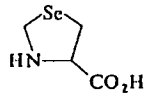
Structure and name	References
XIV-1 W = 3-Me	Mauger *et al.*, 1966
XIV-2 W = 4-Me	Dalby *et al.*, 1962
XIV-3 W = 5-Me	Overberger *et al.*, 1972
XIV-4 W = 4,4-di-Me	Shirota *et al.*, 1977a
XIV-5 W = 4-F	Gerig and McLeod, 1973
XIV-6 W = 4,4-di-F	Shirota *et al.*, 1977a
XIV-7 W = 4-Br	Wieland *et al.*, 1977b
XIV-8 W = 4-Cl; 4-Br; 4-NH_2	Andreatta *et al.*, 1967
XIV-9 W = 3,4-Dehydro	Dormoy *et al.*, 1980; Scott *et al.*, 1980, Fisher *et al.*, 1978; Moore *et al.*, 1977a; Corbella *et al.*, 1969; Robertson and Witkop, 1962
XIV-10 W = 3,4-Dehydro; 4-OH; 4-Me	Felix *et al.*, 1973; McGee *et al.*, 1973
XIV-11 W = 4-Methylene	Bethell and Kenner, 1965; Burgstahler *et al.*, 1964; Wittig *et al.*, 1958
XIV-12 W = 4-SH	Eswarakrishnan and Field, 1981
XIV-13 W = 4-S-*p*-OMe-Bzl	Verbiscar and Witkop, 1970
XIV-14 W = 4-CH_2OH	Bethell *et al.*, 1963; Burgstahler and Aiman, 1962; Bethell and Kenner, 1965
XIV-15 W = 3-OH	Philip and Robertson, 1977; Irreverre *et al.*, 1962; Ogle *et al.*, 1962; Sheehan and Whitney, 1962
XIV-16 W = 4-OH	Lee and Kaneko, 1973a; Hara *et al.*, 1981
XIV-17 W = 3-OH, 5-Me	Mauger and Stuart, 1977

Structure and name	References
XIV-18 W = 3,4-di-OH	Kahl and Wieland, 1981; Adams, 1976; Hudson *et al.*, 1968, 1975
XIV-19 W = 3-OPh	Haeusler and Schmidt, 1979
XIV-20 W = 3,4-Epoxy	Hudson *et al.*, 1968, 1975
XIV-21 W = 2-NH_2; 5-NH_2	Gallina *et al.*, 1970
XIV-22 W = 3-$NHCO_2R$	Haeusler, 1981
XIV-23 W = 4-CN-5-Me-5-CO_2H; 4-CO_2Me-5-Me-5-CO_2H	Casella *et al.*, 1979
XIV-24 W = 4-CO_2H-5-*p*-HOC_6H_4	Belokon *et al.*, 1977
XIV-25 W = 4-Adeninyl, guaninyl, hypoxanthinyl	Kaspersen and Pandit, 1975
XIV-26  2-Aziridinecarboxylic acid	Okawa *et al.*, 1982; Okawa and Nakajima, 1981; Nakajima *et al.*, 1978; Harada and Nakamura, 1978
XIV-27  2-Azetidinecarboxylic acid	Barber *et al.*, 1979; Vičar *et al.*, 1977; Felix *et al.*, 1973; McGee *et al.*, 1973
XIV-28  4-Methyl-2-azetidinecarboxylic acid	Soriano *et al.*, 1980
XIV-29  Pipecolic acid	Balaspiri *et al.*, 1972; Neubert *et al.*, 1972

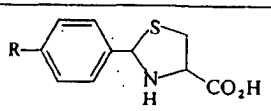
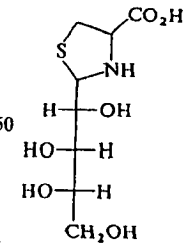
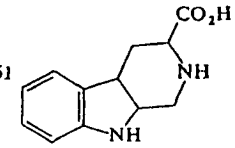
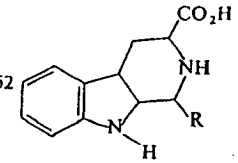
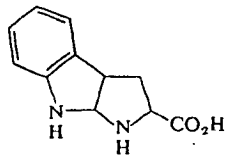
Structure and name	References
XIV-30  1,2,3,6-Tetrahydropicolinic acid	Greenstein and Winitz, 1961
XIV-31  Various azacycloalkane-2-carboxylic acids n = 7, 8, 9, 10, 11 n = 12, 13, 14, 15	Nagasawa *et al.*, 1971; Nagasawa and Elberling, 1966 Elberling and Nagasawa, 1972
XIV-32  3,4-Methyleneproline (5-azabicyclo[3.1.0]hexane-4-carboxylic acid)	Fujimoto *et al.*, 1971
XIV-33  2,4-Methyleneproline (5-azabicyclo[2.1.1]hexane-1-carboxylic acid)	Hughes *et al.*, 1980; Pirrung, 1980
XIV-34  4-Aminopipecolic acid	Schenk and Schütte, 1961
XIV-35  5-Hydroxypipecolic acid	Greenstein and Winitz, 1961

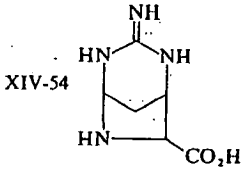
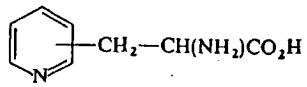
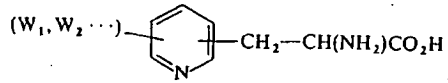
(continued)

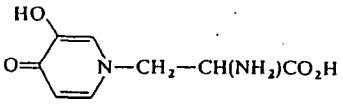
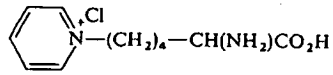
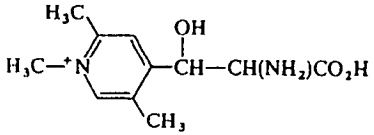
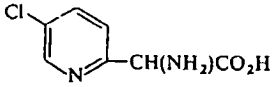
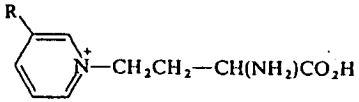
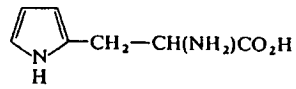
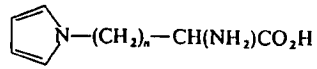
Structure and name	References
XIV-36  4,5-Dihydroxypipecolic acid	Marlier *et al.*, 1972
XIV-37  5,6-Dihydroxy-2,3-dihydroindole-2-carboxylic acid	Büchi and Kamikawa, 1977; Wyler and Chiovini, 1968
XIV-38  1,2,3,4-Tetrahydroquinoline-2-carboxylic acid	Zecchini and Paradisi, 1979
XIV-39  6,7-Dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	Bell *et al.*, 1971
XIV-40  6-Hydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	Müller and Schütte, 1968
XIV-41  6,7-Dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	Daxenbichler *et al.*, 1972

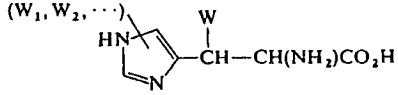
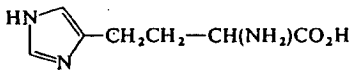
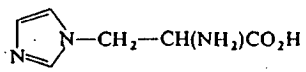
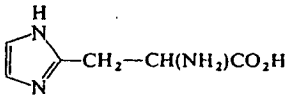
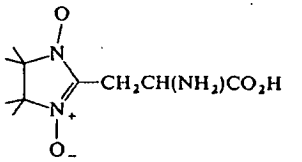
Structure and name	References
XIV-42  1,3-Oxazolidine-4-carboxylic acid	Wolfe *et al.*, 1979
XIV-43  1,2-Oxazolidine-3-carboxylic acid	Vasella and Voeffray, 1981
XIV-44  Perhydro-1,4-thiazine-3-carboxylic acid	Daebritz and Virtanen, 1965; Carson and Wong, 1964
XIV-45  Thiazolidine-4-carboxylic acid	Barber and Jones, 1977; Felix *et al.*, 1973; McGee *et al.*, 1973; Ratner and Clark, 1937
XIV-46  2,2-Dimethylthiazolidine-4-carboxylic acid	Sheehan and Yang, 1958
XIV-47  Perhydro-1,3-thiazine-2-carboxylic acid	Foppoli *et al.*, 1980
XIV-48  Selenazolidine-4-carboxylic acid	DeMarco *et al.*, 1977

(continued)

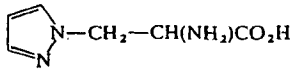
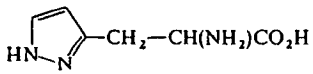
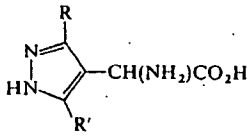
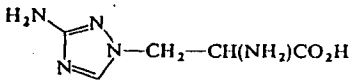
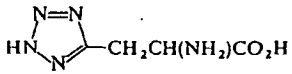
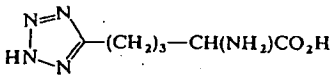
Structure and name	References
XIV-49  2-Phenyl- and 2-(*p*-tolyl)thiazolidine-4-carboxylic acid R = H, Me	Szilagyi and Gyorgydeak, 1979
XIV-50  Arabinose cysteine thioaminal	Bognar *et al.*, 1976
XIV-51  1,2,3,4,4*a*,9*a*-Hexahydro-*β*-carboline-3-carboxylic acid	Yabe *et al.*, 1978
XIV-52  1-(4-Dimethylaminophenyl)-1,2,3,4,4*a*,9*a*-hexahydro-*β*-carboline-3-carboxylic acid R = 4-$Me_2NC_6H_4$	Pindur, 1978
XIV-53  2,3,3*a*,8*a*-Tetrahydropyrrolo(2,3*b*)indole-2-carboxylic acid	Taniguchi and Hino, 1981; Nakagawa *et al.*, 1981

Structure and name	References
XIV-54  6-Imino-2,5,7-triazabicyclo[3.2.1]octane-3 carboxylic acid	Wakamiya *et al.*, 1981
Heterocyclic: pyridine-derived (XV)	
3-(Pyridyl)alanines (some references also to *N*-oxides) 	
XV-1 2-Pyridyl	Veselova and Chaman, 1973: Sullivan *et al.*, 1968; Watanabe *et al.*, 1968
XV-2 3-Pyridyl	Voskuyl-Holtkamp and Schattenkerk, 1979; Sullivan *et al.*, 1968
XV-3 4-Pyridyl	Hoes *et al.*, 1979; Sullivan *et al.*, 1968
Substituted pyridylalanines 	
XV-4 W = 2-Br-3, 4-, 5-, or 6-pyridyl; 2-Cl- 3-, 4-, 5-, or 6-pyridyl	Sullivan and Norton, 1971
XV-5 W = 2-F-3-, 5-, or 6-pyridyl; 1,2-di-hydro-2-oxo-3-, 4-, 5-, or 6-pyridyl	Sullivan *et al.*, 1971
XV-6 W = 5-OH-2-pyridyl	Norton *et al.*, 1961
XV-7 W = 4,5-di-OH-2-pyridyl	Norton and Sanders, 1967
XV-8 W = 5-OH-6-I-2-pyridyl	Norton and Sullivan, 1970

Structure and name	References
XV-9 	Harris, 1976a; Spencer and Notation, 1962 Harris and Teitei, 1977
3-(3-Hydroxy-4-oxo-1,4-dihydro-1-pyridyl)alanine analogs	
XV-10 	Hardy *et al.*, 1976
N-(5-Carboxy-5-aminopentyl)pyridinium chloride	
XV-11 	Thanassi, 1970
1,2,5-Trimethyl-4-(2-amino-2-carboxy-1-hydroxyethyl)pyridinium salt	
XV-12 	Edgar *et al.*, 1979
2-(5-Chloro-2-pyridyl)glycine	
XV-13 	Noguchi *et al.*, 1968
N-(3-Amino-3-carboxypropyl)pyridinium salts	
R = H, COO^-	
See also structure V-11	
Heterocyclic: 3-azolylalanines and related compounds (XVI)	
XVI-1 	Hanck and Kutscher, 1964
3-(2-Pyrryl)alanine	
XVI-2 	Poduška *et al.*, 1969
n = 1, 2, 3	
2-Amino-ω-(1-pyrryl)alkanoic acids	

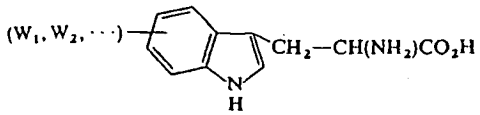
Structure and name	References
Substituted histidines	
	
XVI-3 W = β-Me; β-Et; β-*n*-hexyl	Kelley *et al.*, 1977
XVI-4 W = 4-NO_2; 4-Me; 2-Me	Trout, 1972
XVI-5 W = 4-F	Kirk and Cohen, 1971
XVI-6 W = β-OH	Hecht *et al.*, 1979
XVI-7 W = 2-F; 2-NH_2; 2—N=N—C_6H_4βr	Nagai *et al.*, 1973
XVI-8 W = 1-Me-2-NO_2; 1-Me-4-NO_2; 1-Me-5-NO_2	Tautz *et al.*, 1973
XVI-9 W = 2-SH	Greenstein and Winitz, 1961
XVI-10 2-$SCH_2CH(NH_2)CO_2H$	Ito *et al.*, 1981
XVI-11 2-*p*-N=NPhCO_2H, 4-*p*-N=NPhCO_2H	Montagnoli *et al.*, 1977
XVI-12 	Bloemhoff and Kerling, 1975
Homohistidine	
XVI-13 	Trout, 1972
3-(1-Imidazolyl)alanine	
XVI-14 	Trout, 1972
3-(2-Imidazolyl)alanine	
XVI-15 	Weinkam and Jorgensen, 1971a,b
(1,3-Dioxy-4,4,5,5-tetramethylimidazolin-2-yl)alanine	

(continued)

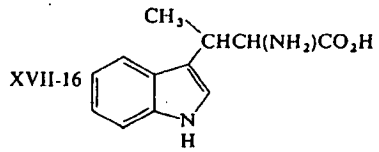
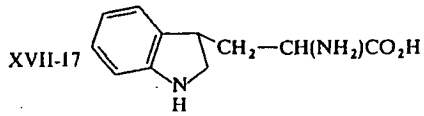
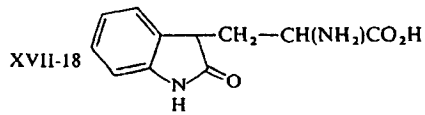
Structure and name	References
XVI-16 	Coy *et al.*, 1975; Murakoshi *et al.*, 1972; Hofmann *et al.*, 1968; Dunnill and Fowden, 1963
3-(1-Pyrazolyl)alanine	
XVI-17 	Seeman *et al.*, 1972; Hofmann *et al.*, 1968; Finn and Hofmann, 1967; Hofmann and Bohn, 1966
3-(3-Pyrazolyl)alanine	
XVI-18 	Ben-Ishai *et al.*, 1978
Substituted α-(4-pyrazolyl)glycines	
R or R′ = Me or Ph	
XVI-19 	Murakoshi *et al.*, 1974
3-(3-Amino-1,2,4-triazol-1-yl)alanine	
XVI-20 	Morley, 1969
β-(Tetrazol-5-yl)alanine	
XVI-21 	Grzonka *et al.*, 1977; Van Thach *et al.*, 1977
2-Amino-4-(5-tetrazolyl)butanoic acid	

Heterocyclic: indolylalanines and other fused hetarylalanines (excluding purines) (XVII)

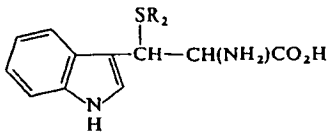
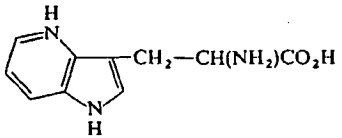
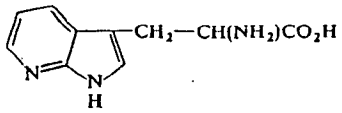
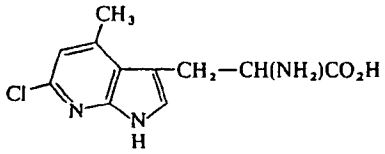
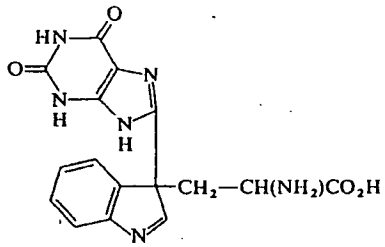
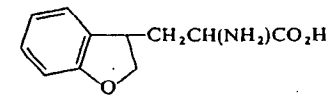
Substituted tryptophans

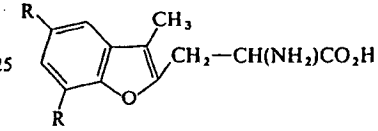
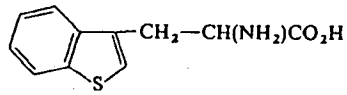
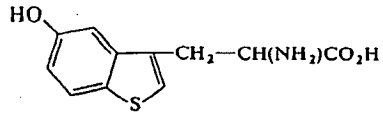
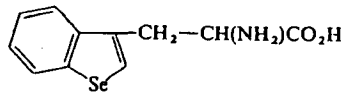
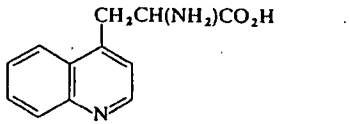
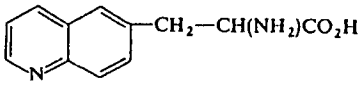
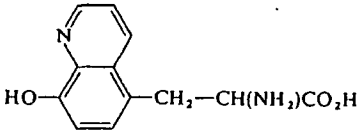


XVII-1 W = 6-Me	Hengartner *et al.*, 1979
XVII-2 W = 4-F; 5-F; 6-F	Bentov and Roffman, 1969

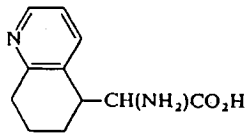
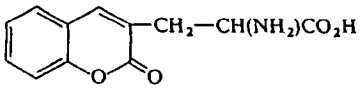
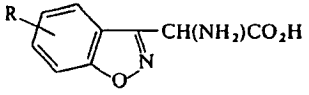
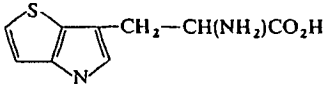
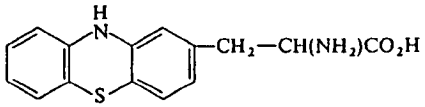
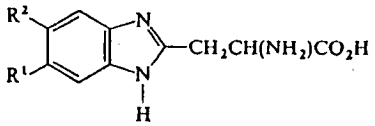
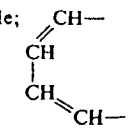
Structure and name	References
XVII-3 W = 5-F; 6-F; 4,5,6,7-tetra-F	Rajh *et al.*, 1979, 1980
XVII-4 W = 5-Cl	Shiba *et al.*, 1975
XVII-5 W = 6-Cl	Moriya *et al.*, 1975
XVII-6 W = 7-Cl	Van Pee *et al.*, 1981
XVII-7 W = 5-Br; 7-Br	Allen *et al.*, 1980
XVII-8 W = 2-OH	Nakazawa *et al.*, 1972
XVII-9 W = 5-OH	Iriuchijima and Tsuchihashi, 1978
XVII-10 W = 7-OH	Greenstein and Winitz, 1961
XVII-11 W = 2-SR	DaSettimo, 1962; Wieland *et al.*, 1974, 1978
XVII-12 W = 6-NH_2	Goodman *et al.*, 1965
XVII-13 W = 6-$N(CH_2CH_2Cl)_2$; 7-$N(CH_2CH_2Cl)_2$; 5-$N(CH_2CH_2Cl)_2$	Goodman *et al.*, 1965; Barclay *et al.*, 1964
XVII-14 W = 4-NO_2; 7-NO_2	Ohno *et al.*, 1974
XVII-15 W = 4-CO_2H	Greenstein and Winitz, 1961
XVII-16 	Greenstein and Winitz, 1961
β-Methyltryptophan	
XVII-17 	Kikugawa *et al.*, 1979; Kikugawa, 1978; Bakhra *et al.*, 1973
2′,3′-Dihydrotryptophan	
XVII-18 	Nakai and Ohta, 1976
2′-Oxo-2′,3′-dihydrotryptophan	

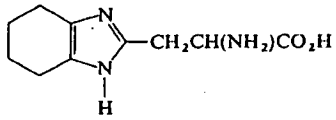
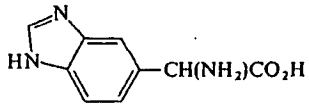
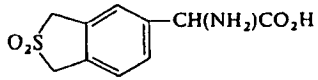
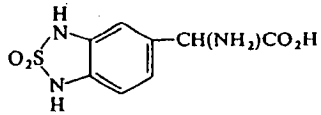
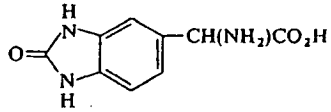
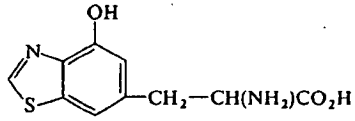
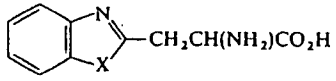
(continued)

Structure and name	References
XVII-19  3-Alkylthiotryptophans	Vinograd *et al.*, 1974
XVII-20  4′-Azatryptophan	Azimov *et al.*, 1968
XVII-21  7′-Azatryptophan	Yabe *et al.*, 1976
XVII-22  6-Chloro-4-methyl-7-azatryptophan	Azimov *et al.*, 1968
XVII-23  3′-(8-Xanthinyl)-3′*H*-tryptophan	Stöhrer *et al.*, 1973
XVII-24  3-(2,3-Dihydrobenzofuran-3-yl)alanine	Rajh *et al.*, 1979

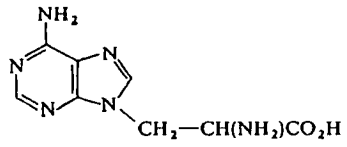
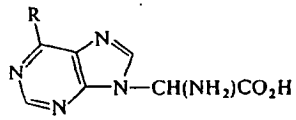
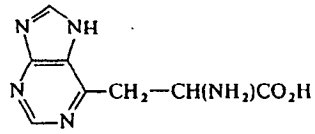
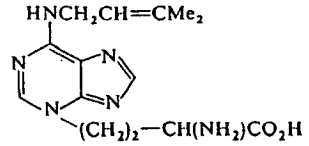
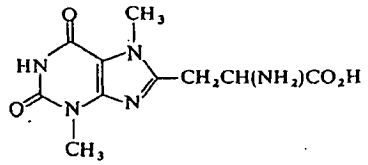
Structure and name	References
XVII-25  3-(3-Methyl-5,7-dialkylbenzofuran-2-yl)alanines	Sila *et al.*, 1973; Sila, 1964
XVII-26  3-(Benzothiophen-3-yl)alanine	Rajh *et al.*, 1979; Yabe *et al.*, 1976
XVII-27  3-(5-Hydroxybenzothiophen-3-yl)alanine	Campaigne and Dinner, 1970
XVII-28  3-(Benzoselenol-3-yl)alanine	Laitem and Christiaens, 1976
XVII-29  3-(4-Quinolyl)alanine	Greenstein and Winitz, 1961
XVII-30  3-(6-Quinolyl)alanine	Berger *et al.*, 1973
XVII-31  3-(8-Hydroxy-5-quinolyl)alanine	Matsumura *et al.*, 1969

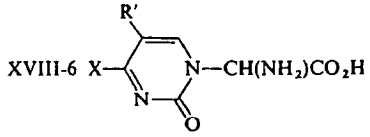
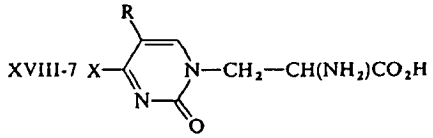
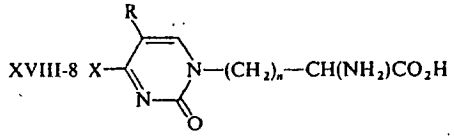
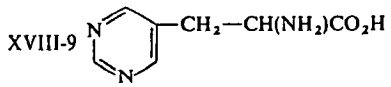
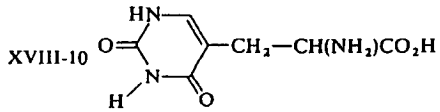
(continued)

Structure and name	References
XVII-32  2-(5,6,7,8-Tetrahydroquinol-5-yl)glycine	Reimann and Voss, 1977
XVII-33  3-(3-Coumarinyl)alanine	Belokon *et al.*, 1977
XVII-34  Substituted 2-(benzisoxazol-3-yl)glycines R = H, 5-Me, 6-Me, 7-Me, 5-Br	Giannella *et al.*, 1972
XVII-35  3-(Thieno-[3,2*b*]pyrrol-3-yl)alanine	Humphries *et al.*, 1972
XVII-36  3-(2-Phenothiazinyl)alanine	Fattorusso, 1965
XVII-37  Substituted benzimidazol-2-ylalanines R^1, R^2 = H, H; Cl, Cl; Me, Me; 	Nestor *et al.*, 1982b

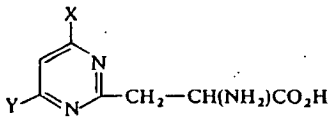
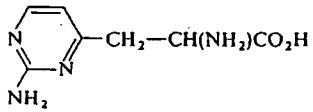
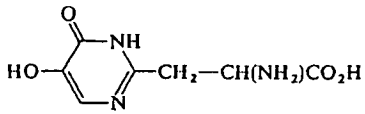
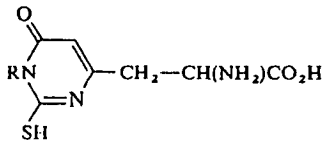
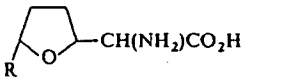
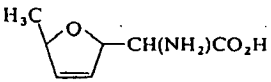
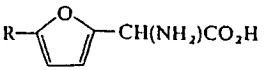
Structure and name	References
XVII-38  4,5,6,7-Tetrahydrobenzimidazol-2-ylalanine	Nestor *et al.*, 1982b
XVII-39  2-(Benzimidazol-5-yl)glycine	Milkowski *et al.*, 1970
XVII-40  2-(1,3-Dihydro-2,2-dioxoisobenzothiophen-5-yl)glycine	Edwards, 1980
XVII-41  2-(1,3-Dihydro-2,2-dioxo-2,1,3-benzothiadiazol-5-yl)glycine	Edwards, 1980
XVII-42  2-(2-Oxobenzimidazol-5-yl)glycine	Edwards, 1980
XVII-43  3-(4-Hydroxybenzothiazol-6-yl)alanine	Ismail *et al.*, 1980
XVII-44  Benzoxazol-2-ylalanines, benzothiazol-2-ylalanines X = O, S	Nestor *et al.*, 1982b

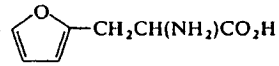
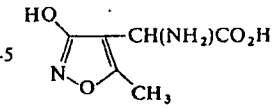
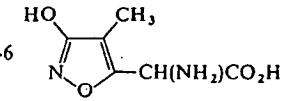
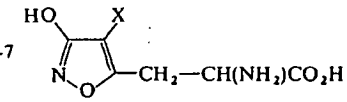
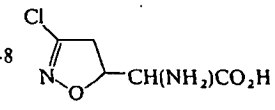
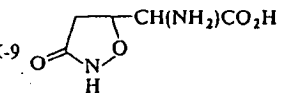
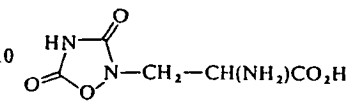
See also structures VII-12; IX-17; XIV-51–53

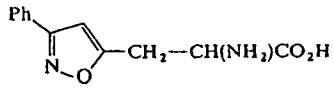
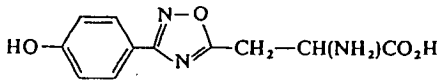
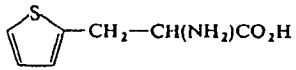
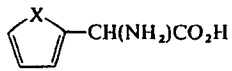
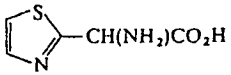
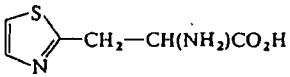
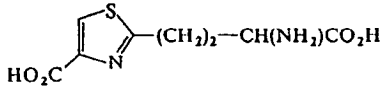
Structure and name	References
Heterocyclic: purine- and pyrimidine-containing (XVIII)	
XVIII-1  3-(9-Adeninyl)alanine, similar amino acids	Shvachkin and Olsuf'eva, 1979; Draminski and Pitha, 1978; Doel *et al.*, 1969, 1974; Nollet and Pandit, 1969a; Lidaks *et al.*, 1968, 1970, 1971a,b; Nollet *et al.*, 1969
XVIII-2  2-(6-Substituted-9-purinyl)glycines R = Cl, NH_2	Nishitani *et al.*, 1979
XVIII-3  3-(6-Purinyl)alanine	Woenckhaus and Stock, 1965
XVIII-4  4-(6-(3-methyl-2-butenylamino)-purin-3-yl)-butyrine	Seela and Hasselmann, 1979; Uchiyama and Abe, 1977; for a related structure see also MacLeod *et al.*, 1975
XVIII-5  3-(8-Theobrominyl)alanine	Vdovina and Karpova, 1968

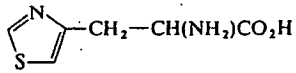
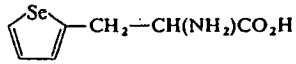
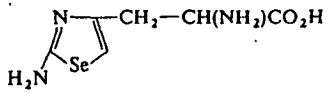
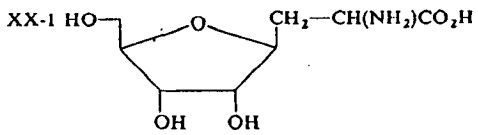
Structure and name	References
XVIII-6  Substituted 2-(1-uracilyl)- and (1-cytosinyl)glycines X = OH or NH_2; R = H, Me, F	Nishitani *et al.*, 1979
XVIII-7  Substituted 3-(1-uracilyl)- and (1-cytosinyl)alanines X = OH or NH_2 Uridine derivative	Shvachkin and Olsuf'eva, 1979; Draminski and Pitha, 1978; Doel *et al.*, 1969, 1974; Lidaks *et al.*, 1971b; Dewar and Shaw, 1962; Martinez *et al.*, 1968 Ohashi *et al.*, 1974
XVIII-8  Substituted 2-amino-ω-(1-pyrimidinyl)alkanoic acids X = OH or NH_2; $n = 2$ X = OH or NH_2; $n = 3, 4, 5$	Nollet and Pandit, 1969b; Tjoeng *et al.*, 1976
XVIII-9  3-(5-Pyrimidinyl)alanine	Haggerty *et al.*, 1965
XVIII-10  3-(6-Uracilyl)alanine (and others)	Vincze *et al.*, 1968; Springer *et al.*, 1965

(continued)

Structure and name	References
XVIII-11 	Shvachkin and Syrtsova, 1963 Shvachkin *et al.*, 1963a,b
Substituted 3-(2-pyrimidinyl)alanines X = Cl, Y = NH_2 X = OH, Y = H	
XVIII-12 	Shvachkin *et al.*, 1968; Whitlock *et al.*, 1965; Shvachkin and Berestenko, 1964
3-(2-Amino-4-pyrimidinyl)alanine	
XVIII-13 	Harris, 1976b
3-(4,5-Dihydroxypyrimidin-2-yl)alanine	
XVIII-14 	Hong *et al.*, 1968
3-(2-Thiouracil-6-yl)alanines	
See also structures VII-28; XII-30; XIV-25; XVII-23	
Heterocyclic: miscellaneous (XIX)	
XIX-1 	Ben-Ishai *et al.*, 1976
2-(5-Alkyl-2-tetrahydrofuryl)glycines	
XIX-2 	Semple *et al.*, 1980; Masamune and Ono, 1975
2-(5-Methyl-2,5-dihydro-2-furyl)glycine	
XIX-3 	Ben-Ishai *et al.*, 1976
2-(5-Alkyl-2-furyl)glycines	

Structure and name	References
XIX-4 	Greenstein and Winitz, 1961
β-(2-Furyl)alanine	
XIX-5 	Christensen and Larsen, 1978
2-(3-Hydroxy-5-methyl-4-isoxazolyl)glycine	
XIX-6 	Hansen and Krogsgaard-Larsen, 1980
2-(3-Hydroxy-4-methyl-5-isoxazolyl)glycine	
XIX-7 	Hansen and Krogsgaard-Larsen, 1980
3-(4-Substituted-3-hydroxy-5-isoxazolyl)alanines X = H, Br, Me	
XIX-8 	Silverman and Holladay, 1981; Kelly *et al.*, 1979; Baldwin *et al.*, 1976
2-(3-Chloro-Δ^2-isoxazolin-5-yl)glycine	
XIX-9 	Silverman and Holladay, 1981; Iwasaki *et al.*, 1969a,b; Kamiya, 1969
2-(3-Oxo-5-isoxazolidinyl)glycine (tricholomic acid)	
XIX-10 	Takemoto *et al.*, 1975
3-(3,5-Dioxo-1,2,4-oxadiazolin-2-yl)alanine	

Structure and name	References
XIX-11  3-(3-Phenyl-5-isoxazolyl)alanine	Vecchio *et al.*, 1963
XIX-12  3-(3-(4-Hydroxyphenyl)-1,2,4-oxadiazol-5-yl)alanine	Moussebois *et al.*, 1977
XIX-13  3-(2-Thienyl)alanine	Lipkowski and Flouret, 1980; Smith *et al.*, 1975, 1978; Bellocq *et al.*, 1977; Sievertsson *et al.*, 1973; Dunn and Stewart, 1971; Hill and Dunn, 1969; Dunn, 1963; du Vigneaud *et al.*, 1945
XIX-14  2-(2-Furyl)glycine, 2-(2-thienyl)glycine X = O, S	Divanfard *et al.*, 1978
XIX-15  2-(2-Thiazolyl)glycine	Hatanaka and Ishimaru, 1973
XIX-16  3-(2-Thiazolyl)alanine	Seto *et al.*, 1974
XIX-17  2-Amino-4-(4-carboxy-2-thiazolyl)-butanoic acid	Jadot *et al.*, 1969

Structure and name	References
XIX-18  3-(4-Thiazolyl)alanine See also compounds IV-22 and VII-28	Watanabe *et al.*, 1966
XIX-19  3-(2-Selenolyl)alanine	Frejd *et al.*, 1980; Jacobs and Davis, 1979
XIX-20  3-(2-Amino-4-selenazolyl)alanine See also structures V-33,44–47; VI-23; VII-9, 29; and XIV-42–50	Hanson and Davis, 1981
Heterocyclic: carbohydrate-containing (XX)	
XX-1  3-(β-Ribofuranosyl)alanine, other carbohydrate containing amino acids See also structures IV-19; V-21; and XIV-50	Rosenthal and Brink, 1976b; Divanfard *et al.*, 1978; Rosenthal and Dooley, 1978; Rosenthal and Ratcliffe, 1977; Rosenthal and Brink, 1976a; Bischofberger *et al.*, 1975; Kum, 1969

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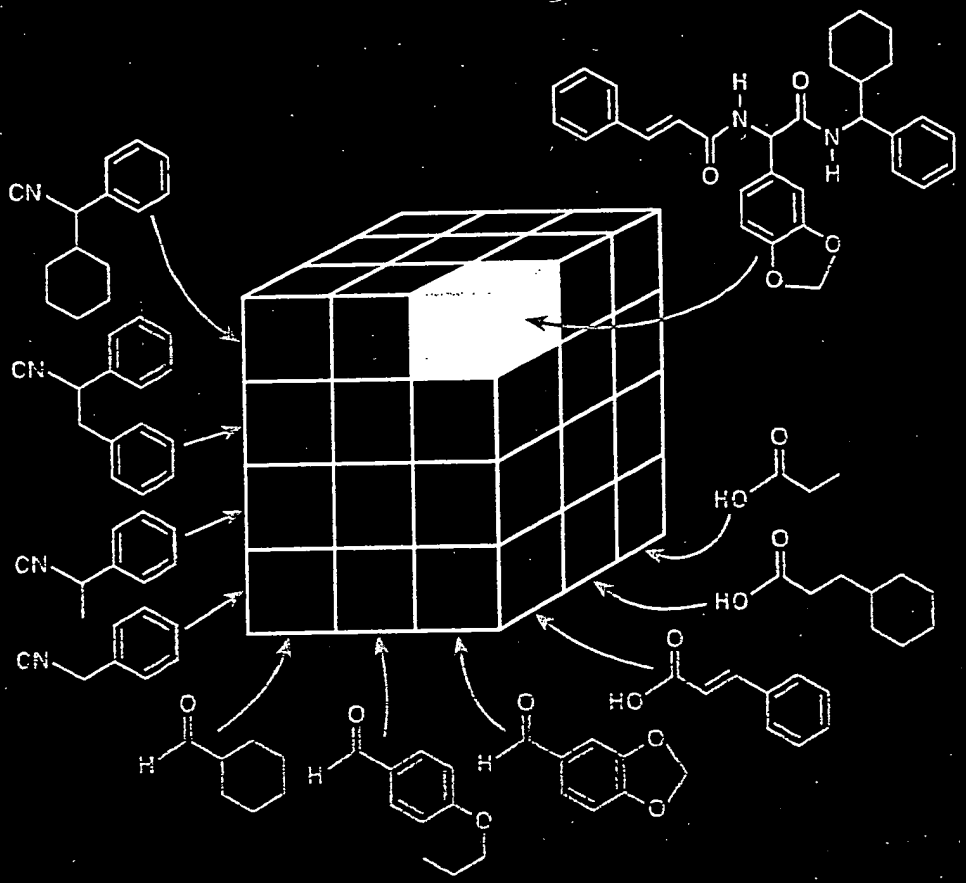
COMBINATORIAL CHEMISTRY

Synthesis and Application



Edited by
Stephen R. Wilson
Anthony W. Czarnik

COMBINATORIAL CHEMISTRY

Synthesis and Application

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IRORI Quantum Microchemistry

A Wiley-Interscience Publication
JOHN WILEY & SONS, INC.
New York • Chichester • Weinheim • Brisbane • Singapore • Toronto

This text is printed on acid-free paper.

Library of Congress Cataloging in Publication Data

Combinatorial chemistry : synthesis and application edited by Stephen R. Wilson and Anthony W. Czarnik.

p. cm.

Includes index.

ISBN 0-471-12687-X (cloth : alk. paper)

1. Combinatorial chemistry. I. Wilson, Stephen R. (Stephen Ross), 1946– . II. Czarnik, Anthony W., 1957–

RS419.C666 1997

615'.19—dc20 96-44718

Printed in the United States of America

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Preface

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CONTENTS

tance to enzymatic degradation (31,32) because of their reduced conformational flexibility. In addition, cyclic peptides have been used for the construction of conformationally defined templates (33). Therefore, this laboratory has prepared a positional scanning cyclic template combinatorial library in which the active compounds were found to be stable to proteolytic enzymes (34).

To circumvent the potential therapeutic limitations relevant to the active compounds found in the L-amino acid libraries, libraries consisting of D- and/or unnatural amino acid peptides have been used to identify active compounds having much greater enzymatic stability (35).

11.4.2 Peptidomimetic Soluble Combinatorial Libraries

The preparation of libraries of oligomeric N-alkylated glycines (13,14), termed peptoids, was the first report of the generation of peptidomimetic libraries. Favorable changes in the physical and chemical properties of the peptidomimetic compounds relative to peptides, such as enhanced resistance to proteolytic enzymes, increased acid stability, favorable aqueous-organic partitioning characteristics, and so forth, are possible with such libraries.

A simpler approach, which greatly expands the diversity of combinatorial libraries, termed the "libraries from libraries" concept, has been developed in our laboratory (15). With this concept, an existing peptide library was exhaustively permethylated while still attached to the solid support used in its synthesis. Since this approach is based on the transformation of a well-defined peptide combinatorial library, and since the chemical transformation is performed using solid-phase methods, equimolarity of the compounds within the peptidomimetic library is easily ensured. A range of chemical transformations can be envisioned to generate a number of peptidomimetic libraries. Thus, a number of peptide libraries, such as those described in Figure 11.7, have been peralkylated using a variety of alkylating agents, including methyl iodide, allyl bromide, and benzyl bromide (36). An example of the chemical structure of one of these peralkylated libraries composed of permethylated hexapeptides is shown in Figure 11.8. The effect of these modifications is that the resulting compounds have very different physical, chemical, and biological properties than their parent compounds. The screening of each peralkylated library in various bioassays led to the identification of highly active compounds derived from completely different parent peptides.

An illustration of the utility of such libraries is presented in Figure 11.9, in which

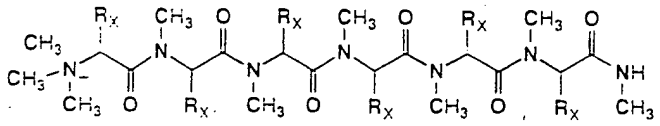

Figure 11.8 N-permethylated hexapeptide combinatorial library. R_x represents the side chains of a mixture of the 20 proteogenic amino acids. The side chains of C, D, E, H, K, N, Q, R, W, and Y have also been modified.

Figure 11.9 Antimicrobial activity against *S. aureus* of the library described in Figure 11.8 when pooled in the positional scanning format. Each individual bar represents the inverse of the IC_{50} value of a permethylated peptide mixture in which the "O" position is defined with one of the 20 proteogenic amino acids.

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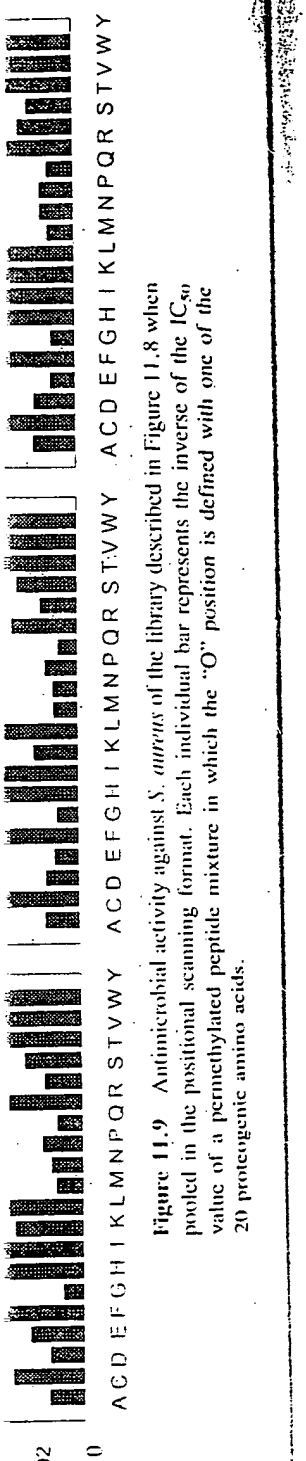
a permethylated positional scanning hexamer library was screened in a standard microdilution assay to identify individual permethylated compounds having potent antimicrobial activity against *Staphylococcus aureus*. Using the structural information from the most active of the 120 permethylated mixtures in this library, 72 individual peptides were synthesized, permethylated, and cleaved. The permethylated form of LFIFFF-NH_2 was found to be the most active compound (IC_{50} = 6 μg/mL and MIC = 11 to 15 μg/mL, where the IC_{50} and MIC values represent the concentrations necessary to inhibit 50 and 100% cell growth, respectively). These compounds showed similar activities against a methicillin-resistant strain of *S. aureus*.

11.4.3 Organic Chemical Libraries

Organic chemical libraries fall into two categories: polymer based and nonpolymer based. In the first category, the synthesis of a small library of oligocarbamates (256 discrete compounds) and its screening against a monoclonal antibody have been reported (37). In our laboratory, polymer-based organic chemical libraries of large diversity have been synthesized using the libraries from libraries approach. The initial application of this concept to form organic libraries was through the generation of a library of substituted polyamines (34 million) (16). To generate the library, a well-characterized hexapeptide library was exhaustively reduced to generate millions of substituted polyamines. This library was found to have substantial activity in both receptor-binding and antimicrobial microdilution assays. Related polyamine libraries have also been synthesized from the exhaustive reduction of peralkylated libraries. Current projects in our laboratory involve the extension of the libraries from libraries concept to form libraries of hydroxylamines, nitrosamines, hydrazines, and so forth.

Advances in the application of chemical reactions to the solid phase initially led to the multiple synthesis (<200 compounds) of discrete nonoligomeric compounds. The synthesis of benzodiazepines (192 compounds) on plastic pins using the microtiter plate format has been reported (17,38), as well as the related syntheses of benzodiazepines and hydantoins (40 compounds) using fritted glass chambers (39). It should be noted that, in each case, these compounds were prepared as discrete products, eliminating the productivity advantage of combinatorial libraries during the assay portion of the process. The feasibility of using pooled combinatorial chemical libraries was first validated by the synthesis of mixtures of β-mercaptoketones (9 compounds) (40) and the synthesis and screening of potential antioxidants (27 compounds) (41). However, validation of the ability of individual assays to distinguish between compounds having the potential for multiple opposing properties remains to be proven when using combinatorial mixtures containing a large diversity of nonpolymeric compounds. The screening of a library consisting of 7600 acylated and alkylated amino acids, which yielded compounds with an affinity for streptavidin, has been reported (42). Similar strategies using diverse chemical reactions such as alkylations, acylations, reductions, and oxidations have been used in our laboratory to sequentially generate large combinatorial libraries (>10,000 com-



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BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Fifth Edition

Volume I: Principles and Practice

Edited by

Manfred E. Wolff

ImmunoPharmaceutics, Inc.
San Diego, California

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS, Inc., New York · Chichester · Brisbane · Toronto · Singapore

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This text is printed on acid-free paper.

Library of Congress Cataloging in Publication Data:

Burger, Alfred, 1905–
[Medicinal chemistry]
Burger's medicinal chemistry and drug discovery. -- 5th ed. / edited by Manfred E. Wolff.
p. cm.
"A Wiley-Interscience publication."
Contents: v. 1. Principles and practice
Includes bibliographical references and index.
ISBN 0-471-57556-9
1. Pharmaceutical chemistry. I. Wolff, Manfred E. II. Title. III. Title: Medicinal chemistry and drug discovery.
RS403.B8 1994
615'. 19--dc20 94-12687

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

CHAPTER FIFTEEN

Molecular Modeling in Drug Design

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CONTENTS

Burger's Medicinal Chemistry and Drug Discovery, Fifth Edition, Volume 1: Principles and Practice, Edited by Manfred E. Wolff.
ISBN 0-471-57556-9

1 INTRODUCTION

By historical imperative, the role of molecular modeling in drug design has been divided into two separate paradigms: one centered on the structure–activity problem, which attempts to rationalize biological activity in the absence of detailed, three-dimensional structural information about the receptor, and the other focused on understanding the interactions seen in receptor–ligand complexes, which uses the known three-dimensional structure of the therapeutic target to design novel drugs. The rapid increase in relevant structural information, as a result of advances in molecular biology that is used to generate the target proteins in adequate quantities for study, and the equally impressive gains in NMR (1–3) and crystallography that provide three-dimensional structures have stimulated the need for design tools, and the molecular modeling community is rapidly evolving useful approaches. The more common problem, however, is one in which the receptor can only be inferred from pharmacological studies and little, if any, structural information is available to guide modeling. Nevertheless, useful information that can guide the design and syn-

etc.) as the macromolecular component, i.e., binding site, of recognition of biologically active small molecules.

4.1 Pharmacophore Versus Binding-site Models

4.1.1 PHARMACOPHORE MODELS. It is often useful to assume that the receptor site is rigid and that structurally different drugs bind in conformations that present a similar steric and electronic pattern, the pharmacophore. Most drugs, because of inherent conformational freedom, are capable of presenting a multitude of three-dimensional patterns to a receptor. This pharmacophoric assumption leads to a problem statement that logically is composed of two processes. The first is the determination, by chemical modification and biological testing, of the relative importance of different functional groups in the drug to receptor recognition. This can give some indication of the nature of the functional groups in the receptor that are responsible for binding the set of drugs. Second, a hypothesis is proposed (Fig. 15.27) concerning correspondence, either between functional groups (pharmacophore) in different congeneric series of the drug or between recognition site points postulated to exist within the receptor (binding-site model).

The intellectual framework for using structure–activity data to extrapolate information regarding the ligand's partner (the receptor) is the concept of the pharmacophore. The pharmacophore, a concept introduced by Ehrlich at the turn of the century, is the critical three-dimensional arrangement of molecular fragments (or the distribution of electron density) that is recognized by the receptor and, in the case of agonists, that causes subsequent activation of the receptor on binding. In other words, some parts of the molecule are essential for interaction, and they must be capable of assuming a particular three-dimensional pattern that is complementary to the receptor to interact favorably. One corollary of the pharmacophoric concept is the ability to replace the chemical scaffold holding the pharmacophoric groups with retention of activity. This is the basis of the current activity in peptidomimetics in which the amide backbone of peptides has been replaced by sugar rings, steroids (249, 250), benzodiazepines (251), or carbocycles (252, 253) (Fig. 15.28). In the pharmacophoric hypothesis, physical overlap of similar functional groups is assumed, i.e., the carboxyl group from compound A physically overlaps with the corresponding

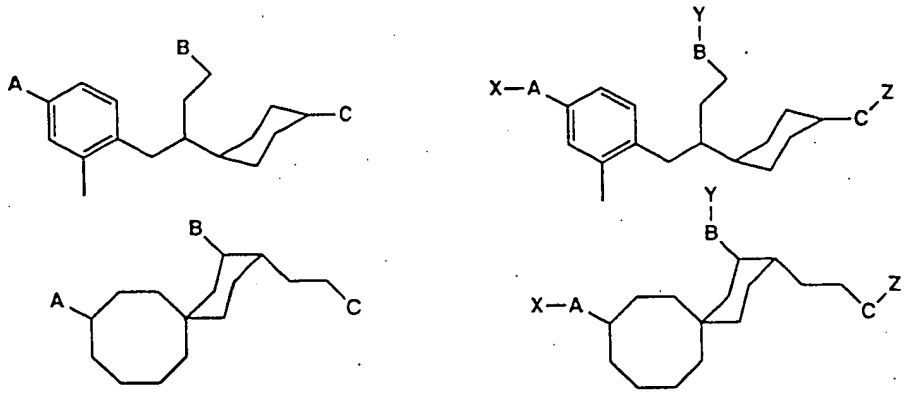
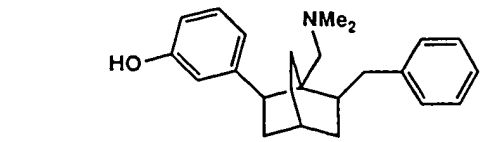
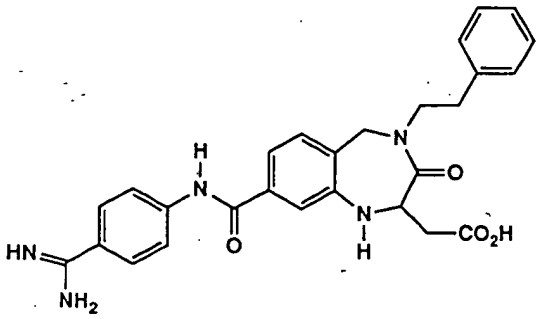


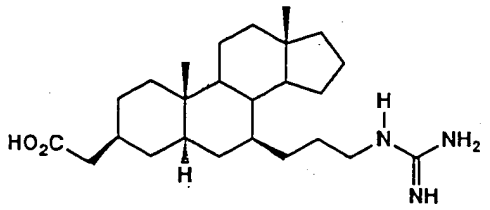
Fig. 15.27 (*a*) Pharmacophore hypothesis with correspondence of functional groups in drugs, A = A′, B = B′, C = C′. (*b*) Binding-site hypothesis using drugs with hypothetical binding sites attached (X, Y, and Z overlap).



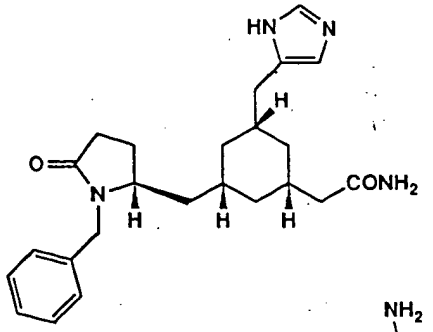
= Tyr-Gly-Gly-Phe-Leu-OH
(Enkephalin)



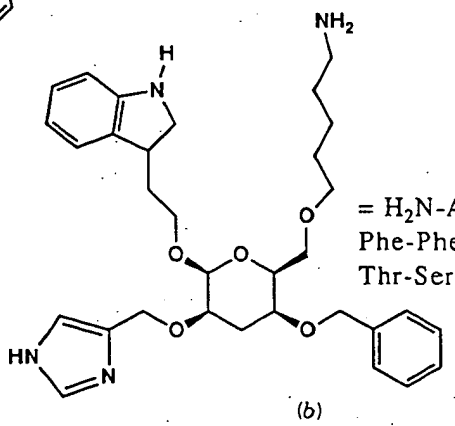
= -Arg-Gly-Asp-
(RGD)



(a)



= Glp-His-Pro-NH_2
(TRH)



= H_2N-Ala-Gly-Cys-Lys-Asn-
Phe-Phe-Trp-Lys-Thr-Phe-
Thr-Ser-Cys-OH
(Somatostatin)

(b)

Fig. 15.28 Peptidomimetics that have been designed based on iterative introduction of constraints into parent peptide and hypotheses concerning receptor-bound conformation. Enkephalin mimetic (254), RGD platelet GPIIb/IIIa receptor antagonists (250, 251), thyroliberin (TRH) (253), and somatostatin (249, 255).

carboxyl group from compound B and with the bioisosteric tetrazole ring of compound C.

One caveat that must be remembered is the probability of alternate or multiple binding modes. The interaction of a ligand with a binding site depends on the free energy of binding, a complex interaction with both entropic and enthalpic components. Simple modifications in structure may favor one of several nearly energetically equivalent modes of interaction with the receptor and change the correspondence between functional groups that has previously been assumed and supported by experimental data. Changes in the binding mode of an antibody Fab fragment to progesterone and its analogs has been shown by crystallography of the complexes (256, 257). For this reason, analysis of agonists as a class is usually preferred, as the necessity to both bind and trigger a subsequent transduction event is more restrictive than the simple requirement for binding shared by antagonists (235). Compounds that clearly are inconsistent with models derived from large amounts of structure–activity data may be indicative of such changes in binding mode and may require a separate structure–activity study to characterize their interaction.

4.1.2 BINDING-SITE MODELS. One major deficiency in the approach described above is the requirement for overlap of functional groups in accord with the pharmacophoric hypothesis. While it is true that molecules having functional groups that show three-dimensional correspondence can interact with the same site, it is also true that a particular geometry associated with one site is capable of interacting with equal affinity with a variety of orientations of the same functional groups. One has only to consider the cone of nearly equal energetic arrangements of a hydrogen-bond donor and acceptor to realize the problem. Sufficient examples from crystal structures of drug–enzyme complexes and from theoretical simulation of binding compel the realization that the pharmacophore is a limiting assumption. Clearly, the observed binding mode in a complex represents the optimal position of the ligand in an asymmetric force field created by the receptor that is subject to perturbation from solvation and entropic considerations. Less restrictive is the assumption that the receptor-binding site remains relatively fixed in geometry when binding the series of compounds under study. Experimental support for such a hypothesis can be found in crystal structures of enzyme–inhibitor complexes in which the enzyme presents essentially the same conformation, despite large variations in inhibitor structures; studies of HIV-1 protease complexed with diverse inhibitors support this view (137). In recent years, therefore, there has been an increasing effort to focus on the groups of the receptor that interact with ligands as being the common features for recognition of a set of analogs. When pharmacophore and binding-site hypotheses are compared, the binding-site model is physicochemically more plausible, because overlap of functional groups in binding to a receptor is more restrictive than assuming the site remains relatively fixed when binding different ligands. However, the number of degrees of freedom in binding-site hypotheses (represented by the necessary addition of virtual bonds between groups A and X, B and Y, and C and Z in Figure 15.27) is greater. Additional degrees of freedom complicate subsequent conformational analyses and may preclude any conclusions, unless a sufficiently diverse set of compounds is available.

Other approaches to this problem have emphasized comparison of molecular properties rather than atom correspondences. Kato et al. (258) developed a program that allows construction of a receptor cavity around a molecule, emphasizing the electrostatic and hydrogen-bonding capa-

bilities. Other molecules can then be fit within the cavity to align them. This is similar in concept to the field-fit techniques available in the CoMFA module of SYBYL, in which the molecular field (electrostatic and steric) surrounding a selected molecule becomes the objective criterion for alignment of subsequent molecules for analysis. An example emphasizing molecular properties in pharmacophoric analysis has been given on inhibitors of cAMP phosphodiesterase II (259).

4.1.3 MOLECULAR EXTENSIONS. If one assumes the binding-site points remain fixed and can augment the drug with appropriate molecular extensions that include the binding site (e.g., a hydrogen-bond donor correctly positioned next to an acceptor), one can then examine the set of possible geometric orientations of site points to see if one is capable of binding all the ligands. Here, the basic assumption of rigid site points is more reasonable, at least for enzymes that have evolved to catalyze reactions and must, therefore, position critical groups in a specific three-dimensional arrangement to create the correct electronic environment for catalysis. The program checks this hypothesis by determining if one or more geometrical arrangements of the postulated groups of site points are common to the set of active compounds. Such a geometrical arrangement of receptor groups becomes a candidate binding-site model, which can be evaluated for predictive merit.

In a study of the active site of angiotensin-converting enzyme (ACE) (260), this binding site model was used by incorporating the active site components as parts of each compound undergoing analysis. As an example, the sulfhydryl portion of captopril was extended to include a zinc bound at the experimentally optimal bond length and bond angle for zinc–sulfur complexes (Fig. 15.29). The orientation map (OMAP), which is a multidimensional representation of the interatomic distances between pharmacophoric groups (Fig. 15.30), was based on the distances between binding-site points such as the zinc atom with the introduction of more degrees of torsional freedom to accommodate the possible positioning of the zinc relative to ACE inhibitors such as captopril (262). Analyses of nearly 30 different chemical classes (Fig. 15.31) of ACE inhibitors led to a unique arrangement of the components of the active site postulated to be responsible for binding the inhibitors. The displacement of the zinc atom in ACE to a location more distant from the carboxyl-binding Arg seen in carboxypeptidase A is compatible with the fact that ACE cleaves dipeptides from the C-terminus of peptides whereas carboxypeptidase A cleaves single amino acid residues.

Visualization of the OMAP is useful to judge the additional information intro-

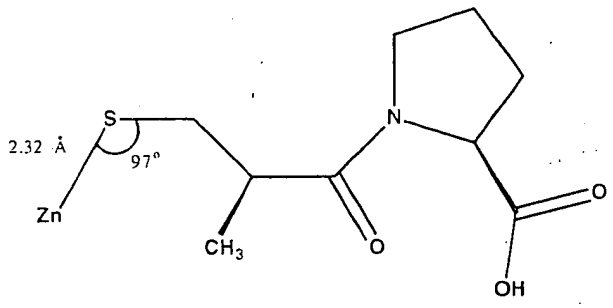
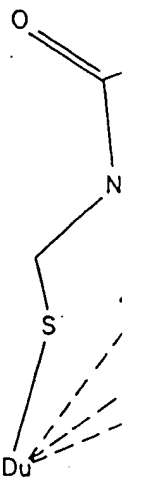


Fig. 15.29 Extension of sulfhydryl group of captopril to include postulated active site zinc, using optimal bond length and angles (260, 261).



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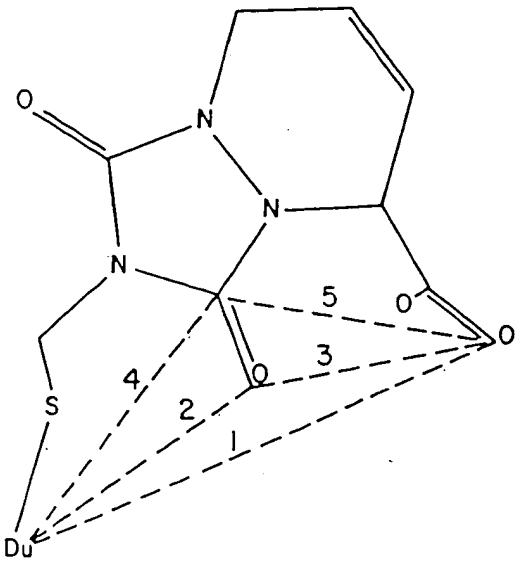


Fig. 15.30 Distances used in five-dimensional OMAP for analysis of ACE inhibitors (260).

duced as each new compound is added (Fig. 15.32). Computationally, it is much more efficient to treat the set of non-congeneric compounds simultaneously (77, 263), but it is reassuring when identical results are obtained if one uses the sequential procedure, introducing each molecule in turn, so that intermediate results may be visually verified. The use of computer graphics to confirm intermediate processing of data in convenient display modes becomes increasingly more important as the individual computations and numbers of molecules under consideration increase.

4.1.4 ACTIVITY VERSUS AFFINITY. Given a consistent model of either type, a limitation is that one can only ask if the compound under consideration can present the three-dimensional electronic pattern (pharmacophore) that is the current candidate. In other words, one is limited to predicting the presence or absence of activity, a binary choice. Even the presence of the appropriate pattern is insufficient to ensure biological activity. For example, competition with the receptor for occupied space by other parts of the molecule can inhibit binding and preclude activity. One can, therefore, postulate the following conditions for activity:

1. The compound must be metabolically stable and capable of transport to the site for receptor interaction (interpretation of inactive compounds may be flawed by problems with bioavailability).
2. The compound must be capable of assuming a conformation which will present the pharmacophoric or binding-site pattern complementary to that of the receptor.
3. The compound must not compete with the receptor for space while presenting the pharmacophoric or binding-site pattern.

Once these conditions are met, one can attempt to deal with the potency, or binding affinity. This belongs to the domain of three-dimensional quantitative structure–activity relationships (3D-QSAR) (264); the use of the variant CoMFA (148, 265) on ACE inhibitors will be illustrated at the end of this chapter. Condition 3 allows one to use compounds that are capable of presenting the pharmacophoric pattern but incapable of binding to help determine the location of receptor-occupied space in relation to the pharmacophore (receptor mapping) (266). This allows a crude, low resolution map of the position of the receptor relative to the pharmacophoric elements and indicates in which directions chemical modifications may be productive.

The number and diversity of compounds available for analysis determines the methodology to be used. If there is a limited data set, then the pharmacophoric approach should be assessed first, due to its fewer degrees of freedom. If no pharmacophoric patterns are consistent with the

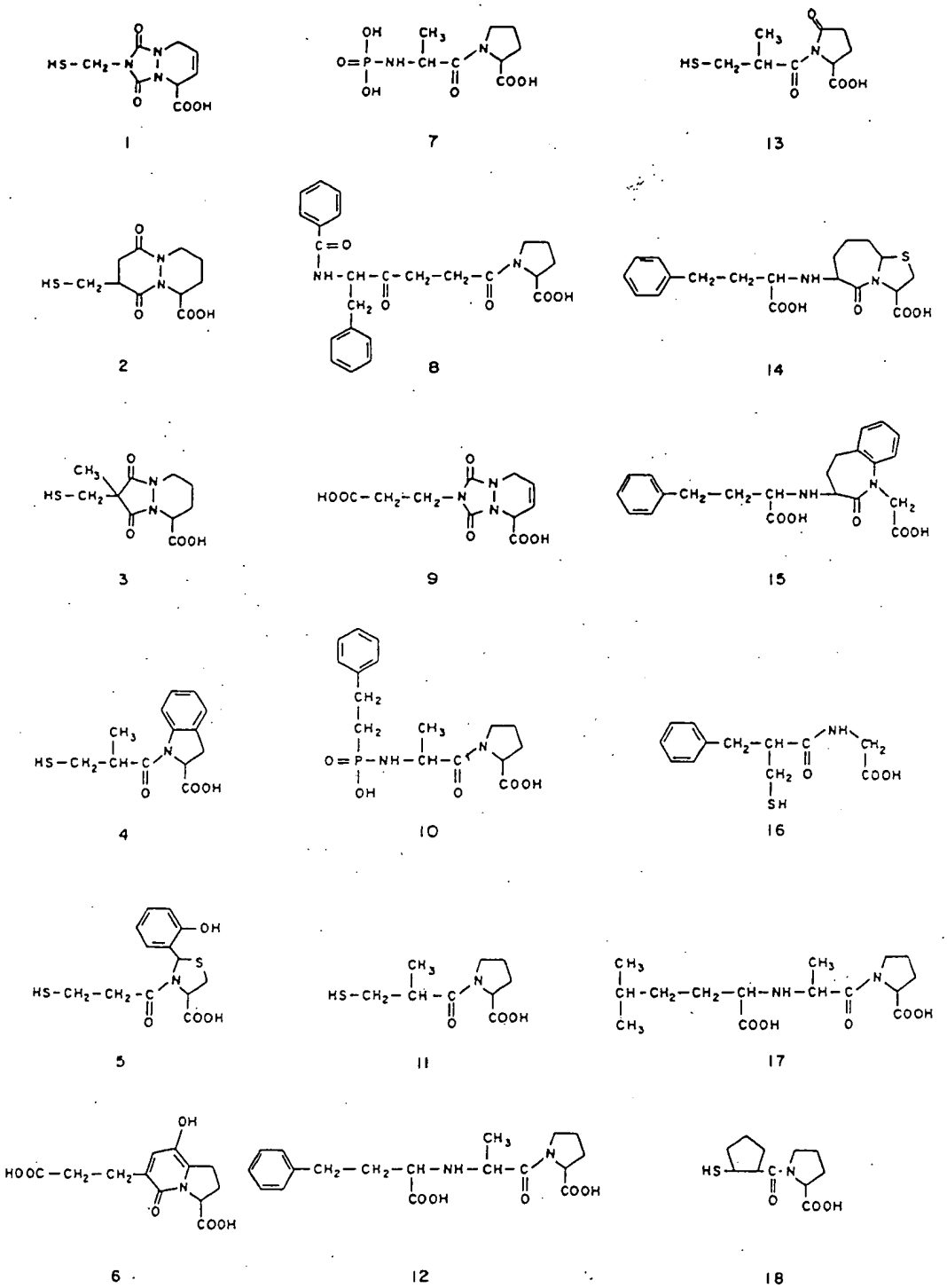
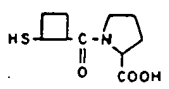


Fig. 15.31 Compounds from different chemical classes of ACE inhibitors used in active site analysis. From Ref. 260.



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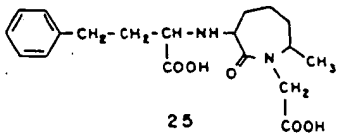

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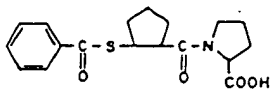

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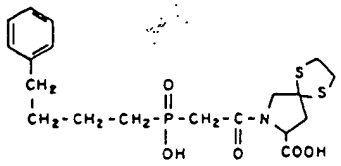

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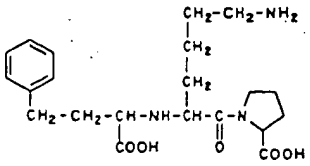

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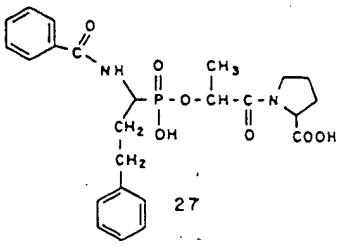

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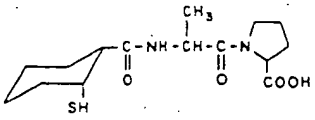

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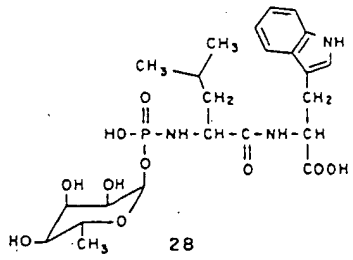

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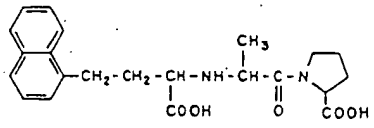

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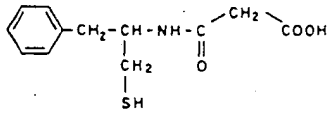

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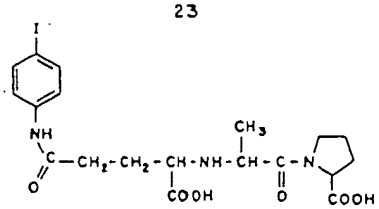

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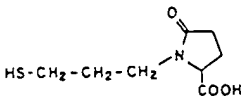

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Fig. 15.31 (*Continued*)

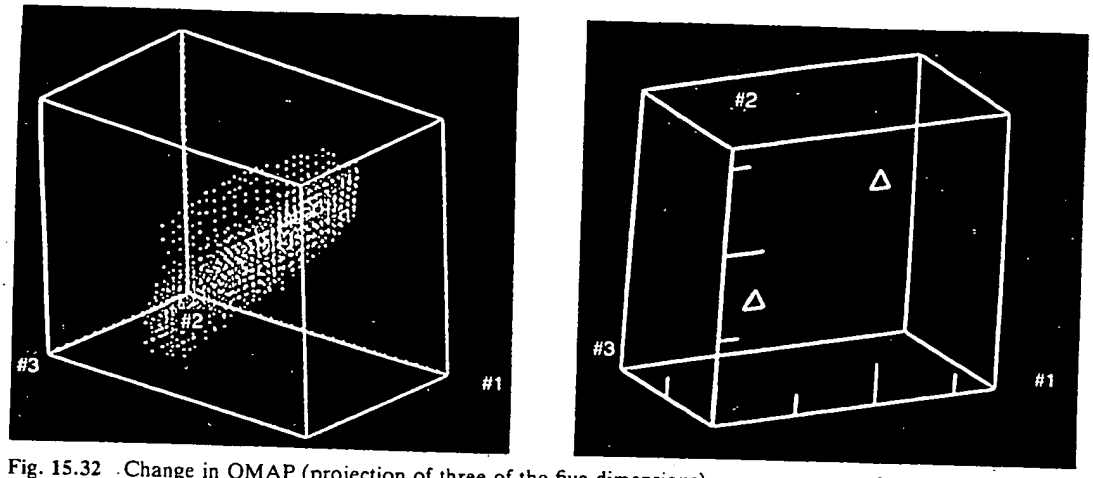

Fig. 15.32 Change in OMAP (projection of three of the five dimensions) as new compounds were introduced to analysis of ACE inhibitors (260). The original OMAP of compound 1 (see Fig. 15.31) is to the left, and the OMAP after completion of analysis is to the right.

set of analogs, then introduction of logical molecular extensions to enable the active site approach is warranted. Operationally, one first determines the set of potential pharmacophoric patterns consistent with the set of active analogs, leading to its name: active analog approach (262). If there are sufficient data, then a unique pharmacophore, or active site model, may be identifiable. The basic assumption behind efforts to infer properties of the receptor from a study of structure–activity relations of drugs that bind is the idea of complementarity. It follows that the stronger the binding affinity, the more likely that the drug fits the receptor cavity and aligns those functional groups that have specific interactions in a way complementary to those of the receptor itself. Certainly, our understanding of intermolecular interactions from studies of known complexes do not dissuade us of this notion but may make us somewhat skeptical of the naive models that often result from such efforts. Andrews et al. (267) have reviewed efforts of this type with regard to CNS drugs.

Clearly, the key to insight relies on chemical modification to determine the relative importance of functional groups for molecular recognition. Often more subtle effects than the simple presence or absence of a group are important, and then comparison of molecular properties becomes of interest. A major impediment to analysis is the definition of a common frame of reference by which to align molecules for comparison. This is equivalent to solving the three-dimensional pharmacophoric pattern and implies that one has distinguished those properties of the molecules under consideration in a manner similar to the receptor. Initial efforts to rationalize structure–activity relationships (SAR) among noncongeneric systems was hampered by an "RMS mentality," i.e., a point of view that required atomic centers to align rather than to overlap with steric and electronically similar groupings. An example would be requiring the six atoms of aromatic benzene rings to overlap at each of the six atoms of the ring vertices rather than the simple requirements for coincidence and coplanarity, which would recognize the torus of electron density that the rings share in common (Fig. 15.33). In congeneric series, the difficulties in assignment of correspondence is less (nonexistent by defini-

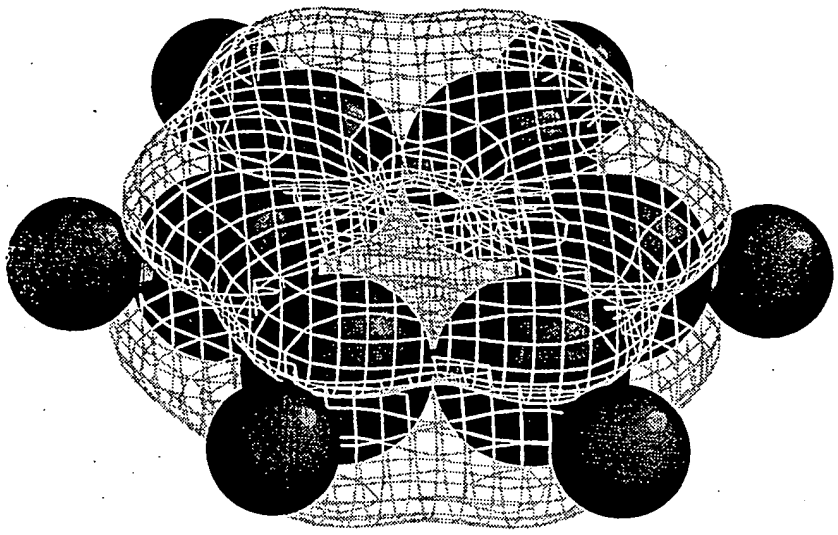

Fig. 15.33 Torus of electron density representing a benzene ring. Atom-to-atom correspondences of ring atoms used in normal fitting routines lead to overconstrained fits.

tion). This allows a variety of approaches, including those based on molecular graph theory (268–271), to detect similarities between molecules, which can form the basis of a correlation analysis. Extrapolation outside of the group of congenerically related compounds on which the analysis was based would appear difficult, if not impossible.

While it is simpler to start an analysis with a congeneric series to identify the recognition elements, diversity in chemical structures implies more information regarding the conformational requirements of the system. A congeneric series requires that the basic chemical framework of the molecule remains constant and that groups on the periphery are either modified (e.g., aromatic substitution) or substituted (e.g., tetrazole for carboxyl functional group). Implicit in this concept is the notion that the compounds bind to the receptor in a similar fashion, and therefore, the changes are localized and comparable for each position of modification. Introduction of degrees of freedom in the substituents and consideration of differences in properties that are conformationally dependent, such as the electric field, require conformational analysis in an effort to determine the relevant conformation for comparison.

The problem can be divided into two: what are the aspects of the molecules that are in common and that may provide the basis for molecular recognition, and which conformation for each molecule is appropriate to consider? For the first problem, studies on a congeneric series can often yield valuable insight. For determination of the three-dimensional arrangement of the crucial recognition elements, diversity in the chemical scaffolds imposes different constraints on possible three-dimensional patterns and generates an opportunity for determining a unique solution.

4.2 Searching for Similarity

4.2.1 SIMPLE COMPARISONS. To gain insight into molecular recognition, subtle differences in molecules must be perceived. Comparisons can be divided into two categories: those that are independent of the orientation and position of the molecule and those that depend on a known